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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/265,191	03/10/1999	DENNIS A. CARSON	07340/044002	4241

7590 07/29/2002

PAULA A BORDEN
BOZICEVIC, FIELD AND FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	37

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

these cells to *IFN*-gam[redacted]producers. Additional targets [redacted] methylation outside the transcriptional control regions of the *IFN*-gamma genetic locus were found to be hypomethylated in Th2 cells but not in Th1 cells. Electrophoretic mobility shift assays (EMSA) revealed at least five distinct protein-DNA complexes that are formed with an *oligonucleotide* containing the *IFN*-gamma promoter TATA proximal regulatory element, and in vitro methylation of this site results in a loss of these three complexes. Furthermore, a comparison of...

...extracts prepared from Th1 and Th2 clones revealed that the EMSA patterns were qualitatively similar but differed quantitatively. In addition, transient transfection of a murine *IFN*-gamma promoter-chloramphenicol acetyl transferase (CAT) gene construct into both Th1 and Th2 clones produced CAT activity that was not inducible by anti-CD3, indicating...
?ds

Set	Items	Description
S1	11	(PREP7) OR (PREP (W)7)
S2	6	RD (unique items)
S3	552	(CPG) AND (IFN OR IL-2 OR TNF)
S4	93	S3 AND (OLIGONUCLEOTIDE)
S5	4	S4 NOT PY>1996

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?logoff
       16jul02 09:20:08 User259876 Session D371.2
            $1.44    0.450 DialUnits File155
               $1.26  6 Type(s) in Format  3
            $1.26  6 Types
     $2.70  Estimated cost File155
            $2.11    0.378 DialUnits File5
               $3.50  2 Type(s) in Format  3
            $3.50  2 Types
     $5.61  Estimated cost File5
            $3.53    0.393 DialUnits File73
               $5.00  2 Type(s) in Format  3
            $5.00  2 Types
     $8.53  Estimated cost File73
            OneSearch, 3 files,  1.220 DialUnits FileOS
     $1.73  TELNET
    $18.57  Estimated cost this search
    $18.94  Estimated total session cost   1.318 DialUnits


### Status: Signed Off. (8 minutes)
```

Status: Path 1 of [Dialog Information Services via Modem]

Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
Status: Signing onto Dialog
 ****
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
Status: Connected

Dialog level 02.05.22D

Last logoff: 14jul02 14:08:29
Logon file001 16jul02 09:12:46
           *** ANNOUNCEMENT ***
                    ***
--U.S. Patents Fulltext (File 654) has been redesigned with
new search and display features. See HELP NEWS 654 for
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                    ***
--Dialog NewsRoom is now available. BEGIN NEWSROOM
to use the files in a OneSearch. See NEW FILES RELEASED
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information.

--CLAIMS/US Patents (Files 340,341, 942) have been enhanced
with both application and grant publication level in a
single record. See HELP NEWS 340 for information.
                    ***
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***TRADEMARKSCAN-Sweden (File 675)
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UPDATING RESUMED
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***CLAIMS/US PATENTS (Files 340, 341, 942)

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***Kompass Western Europe (File 590)
***D&B - Dun's Market Identifiers  (File 516)
***MEDLINE (File 155/154)

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***Washington Post (File 146)
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***Court Filings (File 793)
***Microcomputer Software Guide Online (File 278)
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KWIC is set to 50.
HILIGHT set on as '*'
***                                    ***

File   1:ERIC  1966-2002/Jul 11
       (c) format only 2002 The Dialog Corporation

      Set  Items  Description
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Cost is in DialUnits
?b 155, 5, 73
       16jul02 09:12:56 User259876 Session D371.1
            $0.34    0.098 DialUnits File1
     $0.34  Estimated cost File1
     $0.03  TELNET
     $0.37  Estimated cost this search
     $0.37  Estimated total session cost   0.098 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Jul W1
  File   5:Biosis Previews(R)  1969-2002/Jul W1
         (c) 2002 BIOSIS
  File  73:EMBASE  1974-2002/Jul W1
         (c) 2002 Elsevier Science B.V.
*File  73: For information about Explode feature please
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      Set  Items  Description
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?s (pREP7) or (pREP (w)7)
             11  PREP7
           1982  PREP
        2957778  7
              0  PREP(W)7
      S1      11  (PREP7) OR (PREP (W)7)
?rd
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...completed examining records
S2 6 RD (unique items)
?t s2/3,k/all

2/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10856662 20399864 PMID: 10945767
Nonviral glial cell-derived neurotrophic factor gene transfer enhances survival of cultured dopaminergic neurons and improves their function after transplantation in a rat model of Parkinson's disease.
Bauer M; Meyer M; Grimm L; Meitinger T; Zimmer J; Gasser T; Ueffing M; Widmer H R
Department of Neurology, Klinikum Grosshadern, Ludwig Maximilians Universitat Munchen, Munich, Germany.
Human gene therapy (UNITED STATES) Jul 20 2000, 11 (11) p1529-41, ISSN 1043-0342 Journal Code: 9008950
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... organotypic free-floating roller tube (FFRT) cultures with a vector encoding human glial cell-derived neurotrophic factor (hGDNF). For transfer of an episomal expression vector (*pRep7*-GDNF8) a nonviral, nonliposomal cationic transfection technique was applied and optimized. Recombinant hGDNF expression resulted in a higher number of TH-positive neurons in the ...

2/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10031792 99035167 PMID: 9816319
Prostate-specific membrane antigen: a novel folate hydrolase in human prostatic carcinoma cells.
Pinto J T; Suffoletto B P; Berzin T M; Qiao C H; Lin S; Tong W P; May F; Mukherjee B; Heston W D
Nutrition Research Laboratory, Urology Research Laboratory, Pharmacology Analytical Laboratory, and George M. O'Brien Urology Research Center, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Sep 1996, 2 (9) p1445-51, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA 08748-29; CA; NCI; CA 39203; CA; NCI; DK/CA 47650; DK; NIDDK; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... they react with 7E11-C5 monoclonal antibody. After transfection of PC-3 cells with a full-length 2.65-kb PSM cDNA subcloned into a *pREP7* eukaryotic expression vector, non-PSM antigen-expressing PC-3 cells developed immunoreactivity to 7E11-C5 monoclonal antibody and demonstrated folate hydrolase activities and optimum pH...

2/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08729127 96077143 PMID: 7492311
Synthesis of a Cys949Tyr alpha 2-macroglobulin thiol ester mutant: co-transfection with wild-type alpha 2-macroglobulin in an episomal expression system.
Van Rompaey L; Van den Berghe H; Marynen P

Center for Human [redacted]netics-Flanders Interuniversit[redacted] Institute for Biotechnology, University of Leuven, Belgium.
Biochemical journal (ENGLAND) Nov 15 1995, 312 (Pt 1) p183-90, ISSN 0264-6021 Journal Code: 2984726R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

A full-length alpha 2-macroglobulin (alpha 2M) cDNA was cloned into the episomal expression vectors *pREP7* and pMEP4. Electroporation of the cell lines WI-L2-729HF2, U-937, K-562 and an Epstein-Barr virus-transformed cell line resulted in stable...

2/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07837253 93367247 PMID: 8360497
Induction of antibodies to a kappa V region by gene immunization.
Watanabe A; Raz E; Kohsaka H; Tighe H; Baird S M; Kipps T J; Carson D A
Department of Medicine, University of California, San Diego, La Jolla 92093-0663.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Sep 1 1993, 151 (5) p2871-6, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AR25443; AR; NIAMS; AR41897; AR; NIAMS; CA57868; CA; NCI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... in V regions of several human IgM autoantibodies and is used frequently in chronic lymphocytic leukemia. This gene was inserted into a mammalian expression vector, *pREP7*, to produce pREVk3. Mice injected i.m. with pREVk3 produced antibodies against the V region of Glo, a human monoclonal IgM paraprotein whose kappa L...

2/3,K/5 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12880820 BIOSIS NO.: 200100087969
Improved xenograft function by ex vivo GDNF gene therapy.
AUTHOR: Meyer M(a); Bauer M; Brevig T; Widmer H R; Ueffing M; Zimmer J
AUTHOR ADDRESS: (a)SDU-Odense University, Odense**Denmark
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-2097 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

...ABSTRACT: local delivery to intracerebral grafts has proven difficult. We have been optimizing a non-viral transfection technique (Effectene, Qiagen) for hGDNF gene delivery (plasmid vector *pRep7*-GDNF8) into embryonic (E27) porcine nigral tissue prior to intrastriatal transplantation. Using conditions optimized in vitro, explant cultures were exposed to mitogens (EGF+FGF2) and...
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*pRep7*-GDNF8

2/3,K/6 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06307411 EMBASE No: 1995345521
Synthesis of a Cys949Tyr alphainf 2-macroglobulin thiol ester mutant: Co-transfection with wild-type alphainf 2-macroglobulin in an episomal expression system
Van Rompaey L.; Van den Berghe H.; Marynen P.
Center for Human Genetics, Flanders Interuniv Inst Biotechnol, University of Leuven,Leuven Belgium
Biochemical Journal (BIOCHEM. J.) (United Kingdom) 1995, 312/1 (183-190)
CODEN: BIJOA ISSN: 0264-6021
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

A full-length alphainf 2-macroglobulin (alphainf 2M) cDNA was cloned into the episomal expression vectors *pREP7* and pMEP4. Electroporation of the cell lines WI-L2-729HF2, U-937, K-562 and an Epstein-Barr virus-transformed cell line resulted in stable...
?ds

Set	Items	Description
S1	11	(PREP7) OR (PREP (W)7)
S2	6	RD (unique items)

```
?s (CpG) and (IFN or IL-2 or TNF)
          14221  CPG
         106613  IFN
            700  IL-2
         112273  TNF
      S3     552  (CPG) AND (IFN OR IL-2 OR TNF)
?s s3 and (oligonucleotide)
            552  S3
          85157  OLIGONUCLEOTIDE
      S4      93  S3 AND (OLIGONUCLEOTIDE)
?s s4 not py>1996
             93  S4
        7765209  PY>1996
      S5       4  S4 NOT PY>1996
?t s5/3,k/all
```

5/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09004143 96355018 PMID: 8757335
Macrophages ingest and are activated by bacterial DNA.
Stacey K J; Sweet M J; Hume D A
Centre for Molecular and Cellular Biology, University of Queensland, Brisbane, Australia.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Sep 1 1996, 157 (5) p2116-22, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Recent evidence suggests that bacterial DNA activates immune responses. Here we showed that *TNF*-alpha mRNA was induced in bone marrow-derived macrophages and the macrophage cell line RAW 264 by plasmid DNA, but not by DNaseI-digested plasmid, plasmid methylated on *CpG* dinucleotides, or by vertebrate genomic DNA, which is naturally largely methylated on these sequences. Synthetic polynucleotides poly d(I-C) and poly I x poly C also induced *TNF*-alpha. IL-1 beta and plasminogen activator inhibitor-2 mRNAs

were induced by plasmi[redacted] DNA, and *IFN* -gamma-pretre[redacted]ed macrophages responded to DNA with induction of inducible nitric oxide synthase. The HIV-1 long terminal repeat was activated by exogenous DNA in a manner similar to *TNF*-alpha, and was also activated by a *CpG*-containing *oligonucleotide*. Transcription factor nuclear factor-kappa B (NF-kappa B) is involved in regulation of the HIV-1 long terminal repeat and many inflammatory response genes...

...sufficiently intact to code for luciferase protein. Results suggest that DNA is taken up by macrophages and characteristic bacterial DNA sequences, which include an unmethylated *CpG* sequence, activate a signaling cascade leading to activation of NF-kappa B and inflammatory gene induction. Relevance to DNA vaccination, gene therapy, antisense, and transfection...

5/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08258600 95015849 PMID: 7523497
Differentiation of the T helper phenotypes by analysis of the methylation state of the *IFN*-gamma gene.
Young H A; Ghosh P; Ye J; Lederer J; Lichtman A; Gerard J R; Penix L; Wilson C B; Melvin A J; McGurn M E; et al
Laboratory of Experimental Immunology, NCI-FCRDC, MD.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Oct 15 1994, 153 (8) p3603-10, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Differentiation of the T helper phenotypes by analysis of the methylation state of the *IFN*-gamma gene.
... which CD4+ T cells differentially regulate lymphokine gene expression have not been well defined. In this report, we demonstrate that the methylation status of a *CpG* dinucleotide contained within a TATA proximal regulatory element of the *IFN* -gamma promoter correlates with the transcription of the gene. In murine Th1 clones and two human CD4+ Th0 clones, this site is either completely or...
... this site is > 98% methylated. Treatment of murine Th2 clones with 5-azacytidine, an agent that inhibits methylation of the DNA, converts these cells to *IFN*-gamma producers. Additional targets for methylation outside the transcriptional control regions of the *IFN*-gamma genetic locus were found to be hypomethylated in Th2 cells but not in Th1 cells. Electrophoretic mobility shift assays (EMSA) revealed at least five distinct protein-DNA complexes that are formed with an *oligonucleotide* containing the *IFN*-gamma promoter TATA proximal regulatory element, and in vitro methylation of this site results in a loss of these three complexes. Furthermore, a comparison of...

... extracts prepared from Th1 and Th2 clones revealed that the EMSA patterns were qualitatively similar but differed quantitatively. In addition, transient transfection of a murine *IFN* -gamma promoter-chloramphenicol acetyl transferase (CAT) gene construct into both Th1 and Th2 clones produced CAT activity that was not inducible by anti-CD3, indicating...

5/3,K/3 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09537238 BIOSIS NO.: 199497545608
Differentiation of the T helper phenotypes by analysis of the methylation state of the *IFN*-gamma gene.
AUTHOR: Young Howard A(a); Ghosh Paritosh; Ye Jianping; Lederer James;

Licthman Andrew; Gerard Jeffrey R; Penix Laurei; Wilson Christopher B; Melvin Ann J; et al
AUTHOR ADDRESS: (a)NCI-FCRDC, Build. 560, Room 31-93, Frederick, MD 21702-1201**USA
JOURNAL: Journal of Immunology 153 (8):p3603-3610 1994
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Differentiation of the T helper phenotypes by analysis of the methylation state of the *IFN*-gamma gene.

...ABSTRACT: which CD4+ T cells differentially regulate lymphokine gene expression have not been well defined. In this report, we demonstrate that the methylation status of a *CpG* dinucleotide contained within a TATA proximal regulatory element of the *IFN*-gamma promoter correlates with the transcription of the gene. In murine Th1 clones and two human CD4+ ThO clones, this site is either completely or...

...site is gt 98% methylated. Treatment of murine Th2 clones with 5-azacytidine, an agent that inhibits methylation of the DNA, converts these cells to *IFN*-gamma producers. Additional targets for methylation outside the transcriptional control regions of the *IFN*-gamma genetic locus were found to be hypomethylated in Th2 cells but not in Th1 cells. Electrophoretic mobility shift assays (EMSA) revealed at least five distinct protein-DNA complexes that are formed with an *oligonucleotide* containing the *IFN*-gamma promoter TATA proximal regulatory element, and in vitro methylation of this site results in a loss of these three complexes. Furthermore, a comparison of...

...extracts prepared from Th1 and Th2 clones revealed that the EMSA patterns were qualitatively similar but differed quantitatively. In addition, transient transfection of a murine *IFN*-gamma promoter-chloramphenicol acetyl transferase (CAT) gene construct into both Th1 and Th2 clones produced CAT activity that was not inducible by anti-CD3, indicating...

5/3,K/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

05904623 EMBASE No: 1994319190
Differentiation of the T helper phenotypes by analysis of the methylation state of the *IFN*-gamma gene
Young H.A.; Ghosh P.; Ye J.; Lederer J.; Lichtman A.; Gerard J.R.; Penix L.; Wilson C.B.; Melvin A.J.; McGurn M.E.; Lewis D.B.; Taub D.D.
NCI-FCRDC, Building 560,Frederick, MD 21702-1201 United States
Journal of Immunology (J. IMMUNOL.) (United States) 1994, 153/8 (3603-3610)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Differentiation of the T helper phenotypes by analysis of the methylation state of the *IFN*-gamma gene

...which CD4sup + T cells differentially regulate lymphokine gene expression have not been well defined. In this report, we demonstrate that the methylation status of a *CpG* dinucleotide contained within a TATA proximal regulatory element of the *IFN*- gamma promoter correlates with the transcription of the gene. In murine Th1 clones and two human CD4sup + Th0 clones, this site is either completely or...
...this site is >98% methylated. Treatment of murine Th2 clones with 5-azacytidine, an agent that inhibits methylation of the DNA, converts

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Search Results -

Term	Documents
PREP7.DWPI,TDBD,EPAB,JPAB,USPT,PGPB.	39
PREP7S	0
(PREP7 AND 2).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	38
(L2 AND (PREP7)).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	38

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L3

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DATE: Tuesday, July 16, 2002 Printable Copy Create Case

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DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=AND			
L3	L2 and (pREP7)	38	L3
L2	(pREP?) and (Invitrogen)	651	L2
L1	(pREVk3)	4	L1

END OF SEARCH HISTORY

03551085 EMBASE No: 1988000521

Current contact allergens

AKTUELLE KONTAKALLERGENE

Frosch P.J.
Universitats-Hautklinik, 6900 Heidelberg Germany

H+G Zeitschrift fur Hautkrankheiten (H G Z. HAUTKR.) (Germany) 1987, 62/23 (1631-1638)
CODEN: ZHKRA ISSN: 0301-0481
DOCUMENT TYPE: Journal
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH

...of the positive reactions. The 5 most frequent allergens were nickel sulfate, balsam of Peru, formaldehyde, neomycin sulfate, and cobalt sulfate. Mixed fragrances and Kathon *CG* were among the 20 most frequent allergens though only tested during half of the study period. Glyceril monothioglycolate was the leading *allergen* with hairdressers. Other allergens clinically relevant were rubber gloves, bufexamac, bronopol, and propolis.

DRUG DESCRIPTORS:
**allergen*; *neomycin--adverse drug reaction--ae; *neomycin--drug administration--ad
MEDICAL DESCRIPTORS:
*epidemiology; *patch test; *skin *allergy*

```
?ds

Set     Items   Description
S1        573   (ALLERGY OR ALLERGIC) AND (CPG OR CG OR PREP7)
S2        242   S1 NOT PY>1996
S3          0   S2 AND (IMMUNOTHERAPY OR IMMUNOSTIMULATORY)
S4          0   S2 AND ((GENETIC OR DNA) (W) VACCINE)
S5         54   S2 AND (ALLERGEN OR ANTIGEN)
S6         39   RD (unique items)
?logogg
>>>Invalid set number
?logoff
       19feb03 11:46:15 User259876 Session D466.2
            $1.73    0.540 DialUnits File155
               $2.10  10 Type(s) in Format  3
            $2.10  10 Types
     $3.83  Estimated cost File155
            $0.63    0.214 DialUnits File159
     $0.63  Estimated cost File159
            $2.52    0.450 DialUnits File5
              $12.25  7 Type(s) in Format  3
           $12.25  7 Types
    $14.77  Estimated cost File5
            $7.96    0.884 DialUnits File73
              $55.00  22 Type(s) in Format  3
           $55.00  22 Types
    $62.96  Estimated cost File73
            OneSearch, 4 files,  2.088 DialUnits FileOS
     $1.40  TELNET
    $83.59  Estimated cost this search
    $83.98  Estimated total session cost   2.183 DialUnits


### Status: Signed Off. (6 minutes)
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### Status: Path 1 of [Dialog Information Services via Modem]

### Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
### Status: Signing onto Dialog
 ********
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
### Status: Connected


Dialog level 02.12.60D

Last logoff:  14feb03 16:00:14
Logon file001 19feb03 11:40:45
           *** ANNOUNCEMENT ***
                    ***
--File 515 D&B Dun's Electronic Business Directory is now online
completely updated and redesigned. For details, see HELP NEWS 515.
                    ***
--File 990 - NewsRoom now contains October 2002 to present records.
File 993 - NewsRoom archive contains 2002 records from January 2002-
September 2002. To search all 2002 records, BEGIN 990,993 or B NEWS2002
                    ***
--Alerts have been enhanced to allow a single Alert profile to be
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calendar-based schedule. There are no additional prices for these
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information.
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libraries.  See HELP LIBRARY for more information.
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***
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***TRADEMARKSCAN-Finland (File 679)
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***TRADEMARKSCAN-Norway (File 678)
***TRADEMARKSCAN-Sweden (File 675)
***

UPDATING RESUMED
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***

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***D&B Dun's Electronic Business Directory (File 515)
***U.S. Patents Fulltext 1976-current (File 654)
***Population Demographics (File 581)
***Kompass Western Europe (File 590)
***D&B - Dun's Market Identifiers (File 516)

REMOVED
***Chicago Tribune (File 632)
***Fort Lauderdale Sun Sentinel (File 497)
***The Orlando Sentinel (File 705)
***Newport News Daily Press (File 747)
***U.S. Patents Fulltext 1980-1989 (File 653)
***Washington Post (File 146)
***Books in Print (File 470)
***Court Filings (File 793)
***Publishers, Distributors & Wholesalers of the U.S. (File 450)
***State Tax Today (File 791)
***Tax Notes Today (File 790)
***Worldwide Tax Daily (File 792)

***TOXNET data is added to ToxFile (F156)

New document supplier
IMED has been changed to INFOTRIE (see HELP OINFOTRI)

>>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
>>> of new databases, price changes, etc. <<<
****

KWIC is set to 50.
HILIGHT set on as '*'
* * New CURRENT Year ranges installed **

File 1:ERIC 1966-2003/Jan 22
(c) format only 2003 The Dialog Corporation

Set	Items	Description

Cost is in DialUnits
?b 155, 159, 5, 73
19feb03 11:41:01 User259876 Session D466.1
$0.33 0.095 DialUnits File1
$0.33 Estimated cost File1
$0.06 TELNET
$0.39 Estimated cost this search
$0.39 Estimated total session cost 0.095 DialUnits

SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1966-2003/Feb W2
(c) format only 2003 The Dialog Corp.
File 159:Cancerlit 1975-2002/Oct
(c) format only 2002 Dialog Corporation
***File 159: Updating for Cancerlit has stopped due to end of year** processing.
File 5:Biosis Previews(R) 1969-2003/Feb W3
(c) 2003 BIOSIS
***File 5: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.

File 73:EMBASE 1974-[redacted]3/Feb W2
(c) 2003 Elsevier Science B.V.
***File 73: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.**

```
      Set  Items  Description
      ---  -----  -----------
?s (allergy or allergic) and (CpG or CG or pREP7)
          130872  ALLERGY
          152726  ALLERGIC
           18020  CPG
           13701  CG
              15  PREP7
      S1     573  (ALLERGY OR ALLERGIC) AND (CPG OR CG OR PREP7)
?s s1 not py>1996
             573  S1
         9237854  PY>1996
      S2     242  S1 NOT PY>1996
?s s2 and (immunotherapy or immunostimulatory)
             242  S2
          113860  IMMUNOTHERAPY
            5427  IMMUNOSTIMULATORY
      S3       0  S2 AND (IMMUNOTHERAPY OR IMMUNOSTIMULATORY)
?s s2 and ((genetic or DNA) (w) vaccine)
             242  S2
         1336564  GENETIC
         2095564  DNA
          227614  VACCINE
            4650  (GENETIC OR DNA)(W)VACCINE
      S4       0  S2 AND ((GENETIC OR DNA) (W) VACCINE)
?s s2 and (allergen or antigen)
             242  S2
           53481  ALLERGEN
         1082935  ANTIGEN
      S5      54  S2 AND (ALLERGEN OR ANTIGEN)
?rd
...examined 50 records  (50)
...completed examining records
      S6      39  RD (unique items)
?t s6/3,k/all
```

6/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

09000047 96359725 PMID: 8761084

A new *allergen* dibromodicyanobutane. Report of a study in 310 patients January-December 1994]

Un nouvel allergene: le dibromodicyanobutane. Compte rendu d'une etude portant sur 310 malades de janvier a decembre 1994.

Vigan M; Brechat N; Girardin P; Adessi B; Meyer J P; Vuitton D; Laurent R
Unite d'Allergologie, Service de Dermatologie 2, Hopital Saint-Jacques, Besancon.

Annales de dermatologie et de venereologie (FRANCE) 1996, 123 (5) p322-4, ISSN 0151-9638 Journal Code: 7702013
Document type: Journal Article ; English Abstract
Languages: FRENCH
Main Citation Owner: NLM
Record type: Completed

A new *allergen* dibromodicyanobutane. Report of a study in 310 patients January-December 1994]

INTRODUCTION: Methylisothiazolinone chloride (Kathon *CG*) and its derivatives, used as preservatives in cosmetics, have been shown to be allergenic when used in humans although preliminary studies in Guinea pigs failed...

... battery of the ICDRG [redacted]ttery in patients with contact [redacted]zema. Among the 310 patients tested, 1.94 p. 100 had a positive test for this *allergen* (during this same period, 1.29 p. 100 of the patients were positive for isothiazolinones). Three patients were hospitalized because of generalized eczema and 1 patient had changed occupation with no effect because the crems containing the *allergen* had not been avoided. CONCLUSION: Dibromodicyanobutane is a new *allergen*. Numerous cases of *allergy* have developed as use of the product becomes more widespread. The consequences of this sensitization may have an economic impact. Animal experimentation has been unable...

Descriptors: Allergens--immunology--IM; *Dermatitis, *Allergic* Contact --immunology--IM; *Eczema--chemically induced--CI; *Nitriles --adverse effects--AE; *Preservatives, Pharmaceutical--adverse effects--AE

6/3,K/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08906328 96272538 PMID: 8681539

Methyldibromoglutaronitrile is an important contact *allergen* in The Netherlands.

de Groot A C; de Cock P A; Coenraads P J; van Ginkel C J; Jagtman B A; van Joost T; Joost van der Kley A M; Meinardi M M; Smeenk G; van der Valk P G; van der Walle H B; Weyland J W

Carolus-Liduina Ziekenhuis, Hertogenbosch, The Netherlands.

Contact dermatitis (DENMARK) Feb 1996, 34 (2) p118-20, ISSN 0105-1873 Journal Code: 7604950

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Methyldibromoglutaronitrile is an important contact *allergen* in The Netherlands.

... patch tested with methyldibromoglutaronitrile 0.3%, 0.1% and 0.05% pet. 119 patients (4.0%; women 4.1%, men 3.8%) proved to be *allergic*. 71% of the reactions were considered to be relevant. In 2/3 of the patients, causative products were cosmetics, in 1/3 moistened toilet tissues...
... negative reactions. All preservatives in the European standard series had lower scores than the 4% positive reactions to methyldibromoglutaronitrile (formaldehyde 2.0%, MCI/MI (Kathon *CG*) 3.2%, parabens 1.0%, quaternium-15 1.3%). It is concluded that methyldibromoglutaronitrile (present in the commercial preservative Euxyl K 400) is an important contact *allergen* in the Netherlands in cosmetics and moistened toilet tissues. It should be added to cosmetics series and to proctological series. The optimal test concentration is...

Descriptors: Dermatitis, *Allergic* Contact--etiology--ET; *Nitriles --adverse effects--AE; *Preservatives, Pharmaceutical--adverse effects--AE ; Adolescence; Adult; Aged; Allergens; Child; Dermatitis, *Allergic* Contact--diagnosis--DI; Dose-Response Relationship, Drug; Evaluation Studies; False Negative Reactions; Middle Age; Netherlands; Nitriles --administration and dosage--AD; Patch Tests; Preservatives, Pharmaceutical --administration...

6/3,K/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08678410 96026726 PMID: 8535616

Contact sensitizers modulate mechanisms of receptor-mediated endocytosis but not fluid-phase endocytosis in murine epidermal Langerhans cells.

Becker D; Lempertz U; Enk A; Saloga J; Knop J

Hautklinik der Johannes Gutenberg-Universitat, Mainz, Germany.

Experimental dermatology (DENMARK) Aug 1995, 4 (4 Pt 1) p211-7,

ISSN 0906-6705 Journal Code: 9301549
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... A 3-parameter flow-cytometric technique was performed for quantification of internalized FITC-BSA in LC using quantum red-labeled reagents for detection of Ia-*antigen* expression by LC and propidium iodide for exclusion of dead cells from analysis. A temperature-dependent rapid accumulation of FITC-BSA was noticed in time...

... quantity of FPE under stimulation with phorbol 12-myristate 13-acetate (PMA), concanavalin A (Con A), staphylococcal enterotoxin B (SEB) and contact sensitizers (DNFB, Kathon *CG*, K2Cr2O7) as well as the irritant SLS was determined. Treatment of LC with PMA and Con A resulted in a significant increase of total FITC...
Descriptors: Dermatitis, *Allergic* Contact--pathology--PA; *Langerhans Cells--drug effects--DE; *Pinocytosis--drug effects--DE; Carcinogens --pharmacology--PD; Concanavalin A--pharmacology--PD; Dermatitis, *Allergic* Contact--metabolism--ME; Dinitrofluorobenzene--pharmacology--PD; Fluorescein-5-isothiocyanate--analogs and derivatives--AA; Fluorescein-5-isothiocyanate--metabolism--ME; Mice; Mice, Inbred BALB C; Rhodamines --metabolism...

6/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08632449 95391552 PMID: 7662570
Increasing incidence of contact *allergy* to the new preservative 1,2-dibromo-2,4-dicyanobutane (methyldibromoglutaronitrile).
Van Ginkel C J; Rundervoort G J
Department of Dermatology and Allergology, University Hospital Utrecht, The Netherlands.
British journal of dermatology (ENGLAND) Jun 1995, 132 (6) p918-20, ISSN 0007-0963 Journal Code: 0004041
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Increasing incidence of contact *allergy* to the new preservative 1,2-dibromo-2,4-dicyanobutane (methyldibromoglutaronitrile).
... be positive in the first and second halves of 1993 and the first half of 1994, respectively. In at least 12 of 16 patients this *allergy* was responsible for their presenting complaint (perianal and facial dermatitis). As 12 of 16 patients had intensively used moistened toilet tissues containing this preservative, this habit is presumably the cause of sensitization. Our data indicate that the frequency of sensitization is approaching that of *allergy* to methyl(chloro)isothiazolinone (Kathon *CG* ; 1993: 2.3% in our hospital), a well-known *allergen*, which seems to have been partially replaced in cosmetics and toiletries by this new preservative.
Descriptors: Dermatitis, *Allergic* Contact--etiology--ET; *Ethylene Glycols--adverse effects--AE; *Nitriles--adverse effects--AE; *Preservatives, Pharmaceutical--adverse effects--AE

6/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08558746 95315679 PMID: 7795349
Contact *allergy* in relation to hand eczema and atopic diseases in north

Norwegian schoolchildren.
Dotterud L K; Falk E S
Department of Dermatology, University of Tromso, Norway.
Acta paediatrica (Oslo, Norway : 1992) (NORWAY) Apr 1995, 84 (4) p402-6, ISSN 0803-5253 Journal Code: 9205968
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Contact *allergy* in relation to hand eczema and atopic diseases in north Norwegian schoolchildren.
... was carried out in 424 schoolchildren (223M, 201F), aged 7-12 years, in northern Norway. In 99 (23.3%) of these children, one or more *allergic* patch test reactions were demonstrated; 30 children reacted to two and 6 to three or more substances; 53 irritant reactions were recorded in 33 (7.8%) of those tested. From a total of 144 positive tests, the most common *allergen* was nickel (14.9%), followed by cobalt (5.7%), kathon *CG* (5.2%), lanolin (1.7%) and neomycin (1.4%). Both *allergic* and irritant reactions were found twice as frequently in girls as in boys. Positive patch tests were significantly more frequent in atopic (28.8%) than...

... these 15 subjects, the eczema was localized to the back of the hands, with 13 having atopic dermatitis. In 4 of these 15 children, an *allergic* patch test reaction was found; however, in only 2 of these 4 was the test considered to be clinically relevant for the diagnosis *allergic* hand eczema. In conclusion, irritant hand eczema may occur in early childhood and is most prevalent in children with atopic dermatitis.

6/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07276507 92204267 PMID: 1552971
Replacement of Kathon *CG* by Euxyl K 400 in cosmetics; from the frying pan into the fire?]
Vervangen van Kathon *CG* in cosmetica door Euxyl K 400; van de regen in de drup?
Hulsmans R F; van der Kley A M; Weyland J W; de Groot A C
Carolus Ziekenhuis, afd. Dermatologie, Hertogenbosch.
Nederlands tijdschrift voor geneeskunde (NETHERLANDS) Mar 21 1992, 136 (12) p587-9, ISSN 0028-2162 Journal Code: 0400770
Document type: Journal Article ; English Abstract
Languages: DUTCH
Main Citation Owner: NLM
Record type: Completed

Replacement of Kathon *CG* by Euxyl K 400 in cosmetics; from the frying pan into the fire?]
Vervangen van Kathon *CG* in cosmetica door Euxyl K 400; van de regen in de drup?
The recent negative publicity on the cosmetics preservative Kathon *CG* has made many cosmetic manufacturers look for safer alternatives. The most popular substitute appears to be Euxyl K 400, containing phenoxyethanol and methyldibromoglutaronitrile. Unfortunately, this preservative also induces *allergic* reactions to cosmetics and (at least in the Netherlands) to 'moist toilet paper'. Therefore, in cases of apparent reactions to cosmetics and of eczema ani, *allergy* to methyldibromoglutaronitrile should be suspected. Testing the finished products often results in false-negative reactions, and consequently the *allergen* (suggested concentration 0.05% in petrolatum) should preferably be tested separately.

6/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05925506 88339380 PMID: 3421728

The allergens in cosmetics.

de Groot A C; Bruynzeel D P; Bos J D; van der Meeren H L; van Joost T; Jagtman B A; Weyland J W

Department of Dermatology, Carolus and Willem-Alexander Hospital, 's-Hertogenbosch, The Netherlands.

Archives of dermatology (UNITED STATES) Oct 1988, 124 (10) p1525-9, ISSN 0003-987X Journal Code: 0372433

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The ingredients responsible for *allergy* to cosmetics were determined in 119 patients suffering from cosmetic-related contact dermatitis. Most reactions (56.3%) were caused by skin care products, followed by...

...cosmetics (5.9%). Preservatives were most frequently implicated (32.0%), followed by fragrances (26.5%) and emulsifiers (14.3%). By far the most important cosmetic *allergen* was Kathon *CG* , (a preservative system containing, as active ingredients, a mixture of methylisothiazolinone and methyl chloroisothiazolinone) reacting in 33 patients (27.7%). Other frequent causes of cosmetic-related contact *allergic* reactions were toluenesulfonamide/formaldehyde resin in nail hardener and/or nail lacquer (15 patients [12.6%]), and oleamidopropyl dimethylamine, an emulsifier in baby body lotion...

6/3,K/8 (Item 8 from file: 155)

05728799 88154166 PMID: 3279090

Kathon *CG*: a review.

de Groot A C; Weyland J W

Department of Dermatology, Willem-Alexander Hospital, 's-Hertogenbosch, The Netherlands.

Journal of the American Academy of Dermatology (UNITED STATES) Feb 1988 , 18 (2 Pt 1) p350-8, ISSN 0190-9622 Journal Code: 7907132

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Kathon *CG*: a review.

Kathon *CG*, a cosmetics preservative containing, as active ingredients, 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, appears to be a frequent cause of contact dermatitis in Europe. In the United States, where Kathon *CG* was introduced some 5 years later, the use of this preservative system for cosmetics and toiletries is rapidly increasing. Undoubtedly cases of contact sensitization will soon emerge in this country. Most cases of contact *allergy* are caused by the use of moisturizing creams on (slightly) damaged skin. Sensitization by the use of cosmetic products on previously healthy skin, especially the...

...occur but appears to be less frequent. Rinse-off products do not seem to have a substantial potential for the induction and elicitation of contact *allergic* reactions to Kathon *CG* because of dilution of the product and the *allergen* with water as well as a short contact time with the skin. This review provides a synopsis of current knowledge on the preservative system Kathon *CG* , with emphasis on the risk of sensitization and diagnostic procedures.

6/3,K/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05656015 88082106 PMID: 3691316
Isothiazolinone preservative as important contact *allergen* in cosmetics.
de Groot A C
Department of Dermatology, Willem-Alexander Hospital, 's-Hertogenbosch, Netherlands.
Dermatosen in Beruf und Umwelt. Occupation and environment (GERMANY, WEST) Sep-Oct 1987, 35 (5) p169-73, ISSN 0343-2432 Journal Code: 7802820
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Isothiazolinone preservative as important contact *allergen* in cosmetics.
Kathon *CG* (K-*CG*) containing as active ingredients 2-methyl-4-isothiazolin-3-one and its 5-chloro analogue, is a very effective and widely used preservative system for cosmetics and toiletries. Of 243 patients routinely patch tested because of suspected contact dermatitis 8 (3.3%) reacted to K-*CG* 100 ppm in water. All but 1 patient *allergic* to the preservative used cosmetics of 2 brands very widely distributed in the Netherlands, both containing K-*CG* . The observed positive patch test reactions were shown to be relevant in all these cases. Repeated open application tests were positive in 3/5 of the patients tested. The pertinent literature is reviewed. It is concluded that contact *allergy* to K-*CG* is common. Sensitization usually occurs from creams and lotions applied to damaged skin (irritant dermatitis, atopic dermatitis), but some patients become sensitized by cosmetic products...

6/3,K/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05353502 87104188 PMID: 3492332
Contact *allergy* to preservatives--II.
de Groot A C; Bos J D; Jagtman B A; Bruynzeel D P; van Joost T; Weyland J W
Contact dermatitis (DENMARK) Oct 1986, 15 (4) p218-22, ISSN 0105-1873 Journal Code: 7604950
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Contact *allergy* to preservatives--II.
To determine whether the prevalence of *allergic* reactions to certain preservatives warrants their inclusion in a routine series for patch testing, a tray of 14 preservatives was tested in 501 consecutive suspected contact dermatitis patients. More than 1% positive reactions were found with DMDM hydantoin, Kathon *CG*, and alkyl trimethyl ammonium chloride only. The concentration of alkyl trimethyl ammonium chloride (0.1% aqua) was considered too high. Of 6 patients reacting to the formaldehyde releaser DMDM hydantoin, 4 were positive to formaldehyde. Kathon *CG* may be an important *allergen* in the Netherlands, and it is worthwhile for dermatologists there to add it to the standard test series. The recent inclusion of quaternium-15 in...

6/3,K/11 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10507460 BIOSIS NO.: 199699128605
A new *allergen*: Dibromodicyanobutane. Results of a study in 310 patients, from January to December 1994.
AUTHOR: Vigan M(a); Brechat N; Girardin P; Adessi B; Meyer J P; Vuitton D; Laurent R
AUTHOR ADDRESS: (a)Unite Allergol., Serv. Dermatol. 2, Hopital Saint-Jacques, F-25030 Besancon Cedex**France
JOURNAL: Annales de Dermatologie et de Venereologie 123 (5):p322-324 1996
ISSN: 0151-9638
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: French; Non-English
SUMMARY LANGUAGE: French; English

A new *allergen*: Dibromodicyanobutane. Results of a study in 310 patients, from January to December 1994.

ABSTRACT: Introduction: Methylisothiazolinone chloride (Kathon *CG*) and its derivatives, used as preservatives in cosmetics, have been shown to be allergenic when used in humans although preliminary studies in Guinea pigs failed...
...battery of the ICDRG battery in patients with contact eczema. Among the 310 patients tested, 1.94 p. 100 had a positive test for this *allergen* (during this same period, 1.29 p. 100 of the patients were positive for isothiazolinones). Three patients were hospitalized because of generalized eczema and 1 patient had changed occupation with no effect because the cremes containing the *allergen* had not been avoided. Conclusion: Dibromodicyanobutane is a new *allergen*. Numerous cases of *allergy* have developed as use of the product becomes more widespread. The consequences of this sensitization may have an economic impact. Animal experimentation has been unable...
MAJOR CONCEPTS: *Allergy* (Clinical Immunology, Human Medicine, Medical Sciences...
MISCELLANEOUS TERMS: *ALLERGY* TEST...

6/3,K/12 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10363193 BIOSIS NO.: 199698818111
***Allergic* contact dermatitis from Euxyl K 400 in moist toilet paper.**
AUTHOR: Komericki P(a); Kranke B; Aberer W
AUTHOR ADDRESS: (a)Auenbruggerplatz 8, A-8036 Graz**Austria
JOURNAL: Allergologie 19 (2):p85-87 1996
ISSN: 0344-5062
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: German; English

***Allergic* contact dermatitis from Euxyl K 400 in moist toilet paper.**

...ABSTRACT: 3 fingers of the right hand after using topical ointments against hemorrhoids and moist toilet paper for years. Patch testing proved the trigger of this *allergic* contact dermatitis. Positive test results appeared to the moist toilet paper and its preservative Euxyl K 400. The lesions improved rapidly after topical treatment with glucocorticosteroid ointment and avoiding the *allergen*. This report describes the problems of preserving cosmetics and toilet-articles: preservatives should have a good biocide quality and a low sensitizing potency. Euxyl K 400 matches most points of this assumption. and it replaces more and more the isothiazolinones (e.g. Kathon *CG*) in cosmetics. Nevertheless. in the last years contact dermatitis to this

biocide is seen more often. This is exemplary for the fact that substances with an even low sensitization capacity might frequently lead to *allergic* reactions if the consumer is heavily exposed.
MAJOR CONCEPTS: *Allergy* (Clinical Immunology, Human Medicine, Medical Sciences...

6/3,K/13 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09843003 BIOSIS NO.: 199598297921
Modulation of endocytotic mechanisms as a parameter for predictive testing of contact sensitizers.
AUTHOR: Becker Detlef; Lempertz Uwe; Kuehn Ulrich; Enk Alexander H; Saloga Joachim; Knop Juergen
AUTHOR ADDRESS: Dep. Dermatol., Univ. Mainz, Mainz**Germany
JOURNAL: Journal of Investigative Dermatology 104 (4):p647 1995
CONFERENCE/MEETING: Annual Meeting of the Society for Investigative Dermatology Chicago, Illinois, USA May 24-28, 1995
ISSN: 0022-202X
RECORD TYPE: Citation
LANGUAGE: English

...REGISTRY NUMBERS: KATHON *CG*;
DESCRIPTORS:
MAJOR CONCEPTS: *Allergy* (Clinical Immunology, Human Medicine, Medical Sciences...
CHEMICALS & BIOCHEMICALS: KATHON *CG*;
MISCELLANEOUS TERMS: *ALLERGEN*; ...

...KATHON *CG*;

6/3,K/14 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09820451 BIOSIS NO.: 199598275369
Contact *allergy* in relation in hand eczema and atopic diseases in north Norwegian schoolchildren.
AUTHOR: Dotterud L K(a); Falk E S
AUTHOR ADDRESS: (a)Dep. Dermatology, Univ. Hosp., N-9038 Tromso**Norway
JOURNAL: Acta Paediatrica 84 (4):p402-406 1995
ISSN: 0803-5253
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Contact *allergy* in relation in hand eczema and atopic diseases in north Norwegian schoolchildren.

...ABSTRACT: was carried out in 424 schoolchildren (223M, 201F), aged 7-12 years, in northern Norway. In 99 (23.3%) of these children, one or more *allergic* patch test reactions were demonstrated; 30 children reacted to two and 6 to three or more substances; 53 irritant reactions were recorded in 33 (7.8%) of those tested. From a total of 144 positive tests, the most common *allergen* was nickel (14.9%), followed by cobalt (5.7%), kathon *CG* (5.2%), lanolin (1.7%) and neomycin (1.4%). Both *allergic* and irritant reactions were found twice as frequently in girls as in boys. Positive patch tests were significantly more frequent in atopic (28.8%) than...

...these 15 subjects, the eczema was localized to the back of the hands, with 13 having atopic dermatitis. In 4 of these 15 children, an *allergic* patch test reaction was found; however, in only 2 of these 4

was the test considered to be clinically relevant for the diagnosis *allergic* hand eczema. In conclusion, irritant hand eczema may occur in early childhood and is most prevalent in children with atopic dermatitis.
MAJOR CONCEPTS: *Allergy* (Clinical Immunology, Human Medicine, Medical Sciences...

6/3,K/15 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07872627 BIOSIS NO.: 000041109750
A CASE OF CONTACT *ALLERGY* TO KATHON *CG* IN THE USA
AUTHOR: ZEMTSOV A
AUTHOR ADDRESS: DEP. DERMATOL., TEXAS TECH UNIV. SCH. MED., LUBBOCK, TEX. 79430, USA.
JOURNAL: CONTACT DERMATITIS 25 (2). 1991. 135. 1991
FULL JOURNAL NAME: Contact Dermatitis
CODEN: CODED
RECORD TYPE: Citation
LANGUAGE: ENGLISH

A CASE OF CONTACT *ALLERGY* TO KATHON *CG* IN THE USA
DESCRIPTORS: HUMAN NIVEA MOISTURIZING OIL *ALLERGEN* COSMETICS PRESERVATIVE SKIN CARE

6/3,K/16 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05651892 BIOSIS NO.: 000084000297
A COMPARATIVE STUDY OF THE ALLERGENICITY OF QUATERNARY AMMONIUM COMPOUNDS IN GUINEA-PIGS
AUTHOR: SCHALLREUTER K U; SCHULZ K H
AUTHOR ADDRESS: DEP. DERMATOLOGY, UNIV. MINNESOTA, P.O. BOX 98, 420 DELAWARE ST., S.E., MINNEAPOLIS, MN 55455, USA.
JOURNAL: CLIN EXP DERMATOL 11 (5). 1986 (RECD. 1987). 460-466. 1986
FULL JOURNAL NAME: Clinical and Experimental Dermatology
CODEN: CEDED
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

...ABSTRACT: quats.sbd.the numbers for quats are synonymous with Colipa numbers) and one preservative formula which equilibrates to produce two other quaternary ammonium salts (Kathon *CG*), were tested for their ability to induce *allergic* contact hypersensitivity in guinea-pig. A modified Freunds Complete Adjuvant Test (FCAT) was used, together with the guinea-pig Maximization Test (GPMT), on 10 and 20 animals, respectively. Of the nine substances tested by these methods, two were designated as strong allergens, whereas Kathon *CG* could function as a strong *allergen* at concentrations high enough to provide the quaternary ammonium ion in the equilibrium mixture. Evidence will be presented to support the hypothesis that only those...
DESCRIPTORS: *ALLERGIC* CONTACT HYPERSENSITIVITY *ALLERGEN* IMMUNE RESPONSE ANIMAL MODEL

6/3,K/17 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05248178 BIOSIS NO.: 000082088802
DEMONSTRATION OF KATHON *CG* IN SOME COMMERCIAL PRODUCTS
AUTHOR: GRUVBERGER B; PERSSON K; BJORNER B; BRUZE M; DAHLQUIST I; FREGERT S
AUTHOR ADDRESS: DEP. OF OCCUPATIONAL DERMATOL., UNIV. HOSP., S-221 85 LUND,

SWEDEN.
JOURNAL: CONTACT DERMATITIS 15 (1). 1986. 24-27. 1986
FULL JOURNAL NAME: Contact Dermatitis
CODEN: CODED
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

DEMONSTRATION OF KATHON *CG* IN SOME COMMERCIAL PRODUCTS

ABSTRACT: The preservative Kathon *CG* has become one of the most common sensitizers. It has, however, been difficult to explain the sensitization and to assess the clinical relevance of the contact *allergy*, partly due to lack of specification of the preservative in products. A high-performance liquid chromatography method was used to demonstrate Kathon *CG* in 123 commercial products of both "leave on" and "rinse off" types. 38 of these contained Kathon *CG* in the range of 1-15 ppm of active ingredients. There were no differences between "leave on" and "rinse off" products concerning the relative number of products containing Kathon *CG* and the concentrations of the preservative.
DESCRIPTORS: LEAVE-ON PRODUCTS RINSE-OFF PRODUCTS PRESERVATIVE POSSIBLE CONTACT *ALLERGEN* HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

6/3,K/18 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06475837 EMBASE No: 1996124343
The *allergic* skin
LA PEAU DE L'ALLERGIQUE
Grosshans E.
Clinique Dermatologique, Universite Louis-Pasteur, Faculte de Medecine,67091 Strasbourg Cedex France
Revue du Praticien (REV. PRAT.) (France) 1996, 46/8 (968-973)
CODEN: REPRA ISSN: 0035-2640
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: FRENCH SUMMARY LANGUAGE: FRENCH; ENGLISH

The *allergic* skin

The main cutaneous manifestation of *allergy* is eczema. In atopic dermatitis, the epidermal Langerhans cells express receptors for IgE and the eczematous lesions may be associated with other atopic disorders such as asthma or pollinosis. In contact dermatitis, the epidermal Langerhans' cells play the role of *antigen*-presenting cells; the antigens eliciting the eczematous lesions may be of occupational, vestimentary, cosmetical, therapeutical or other environmental origin. Epicutaneous test procedures enable their identification...
DRUG DESCRIPTORS:
**allergen*--drug toxicity--to; *corticosteroid--drug therapy--dt; *cosmetic--drug toxicity--to; *drug--adverse drug reaction--ae ...adverse drug reaction--ae; clioquinol--adverse drug reaction--ae; cobalt chloride--drug toxicity--to; epoxy resin--drug toxicity--to; hexamidine --adverse drug reaction--ae; kathon *cg*--adverse drug reaction--ae; ketoprofen--adverse drug reaction--ae; lanolin--adverse drug reaction--ae; mercury derivative--adverse drug reaction--ae; neomycin--adverse drug reaction--ae...
MEDICAL DESCRIPTORS:
*contact *allergy*--side effect--si; *contact *allergy*--diagnosis--di; *contact *allergy*--etiology--et; *contact *allergy*--drug therapy--dt; *eczema--diagnosis--di; *eczema--etiology--et; *eczema--drug therapy--dt; *eczema--side effect--si; *skin *allergy*--diagnosis--di; *skin *allergy* --side effect--si; *skin *allergy*--drug therapy--dt; *skin *allergy* --etiology--et
...CAS REGISTRY NO.: 7646-79-9 (cobalt chloride); 3811-75-4 (hexamidine); 55965-84-9 (kathon *cg*); 22071-15-4...

6/3,K/19 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06314915 EMBASE No: 1995352909
Tolerance to different toilet paper preparations: Toxicological and allergological aspects
Blecher P.; Korting H.C.
Dermatologische Klinik Poliklinik, LMU, Frauenlobstrasse 9-11,D-80337 Munchen Germany
Dermatology (DERMATOLOGY) (Switzerland) 1995, 191/4 (299-304)
CODEN: DERAE ISSN: 1018-8665
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...total of 20 patients could be evaluated in full. A variety of reactions were seen in the patch test, most of which were of the *allergic* type. Allergens included many different chemical entities, e.g. preservatives used in moist toilet paper such as Kathon *CG* and Euxyl K 400. In a volunteer *allergic* to Euxyl K 400, *allergy* to the moist toilet paper regularly used by him was established. After discontinuation of its application, perianal dermatitis disappeared. In the repeated rubbing test at...

...type of toilet paper. The validity of these findings was corroborated by corresponding results in the use test. Conclusion: There is clearly a potential for *allergic* reactions to components of moist toilet paper and reactions to recycled toilet paper presumably irritant by nature. These irritant reactions are probably caused by the...
DRUG DESCRIPTORS:
allergen; euxyl k 400--drug toxicity--to; kathon *cg*--drug toxicity--to
MEDICAL DESCRIPTORS:
*contact *allergy*; *eczema; *sanitation
allergic reaction; article; clinical article; clinical trial; female; human; hygiene; male; patch test; priority journal
CAS REGISTRY NO.: 98668-04-3 (euxyl k 400); 55965-84-9 (kathon *cg*)

6/3,K/20 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06243335 EMBASE No: 1995274082
Activation of murine epidermal TCR-gammadeltasup + T cells by keratinocytes treated with contact sensitizers
Huber H.; Descossy P.; Van Brandwijk R.; Knop J.
Klinische Forschergruppe Allergie, Hautklinik Johannes Gutenberg-Univ.,551 31 Mainz Germany
Journal of Immunology (J. IMMUNOL.) (United States) 1995, 155/6 (2888-2894)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...keratinocytes and that stimulated DETC produced, for example, a keratinocyte- specific growth factor. To investigate whether DETC are involved in the induction of a contact *allergy*, we examined the influence of contact sensitizers and nonsensitizing contact irritants on the DETC response toward epidermal symbionts. We show that 9 of 15 cloned...
DRUG DESCRIPTORS:
*t lymphocyte receptor; *1 fluoro 2,4 dinitrobenzene; *diphencyprone; * kathon *cg*; *nickel sulfate; *oxazolone; *picryl chloride; *potassium chromate
cd4 *antigen*--endogenous compound--ec; cd8 *antigen*--endogenous compound

--ec; growth factor--endogenous compound--ec
MEDICAL DESCRIPTORS:
*contact *allergy*; *epidermis cell; *keratinocyte; *t lymphocyte
...CAS REGISTRY NO.: 70-34-8 (1 fluoro 2,4 dinitrobenzene); 886-38-4 (diphencyprone); 55965-84-9 (kathon *cg*); 7786-81-4 (nickel sulfate); 88-88-0 (picryl chloride); 7789-00-6 (potassium chromate)

6/3,K/21 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

05900626 EMBASE No: 1994307838
Reproducibility of patch tests: A multicenter study of synchronous left-versus right-sided patch tests by the German Contact Dermatitis Research Group
Brasch J.; Henseler T.; Aberer W.; Bauerle G.; Frosch P.J.; Fuchs T.; Funfstuck V.; Kaiser G.; Lischka G.G.; Pilz B.; Sauer C.; Schaller J.; Scheuer B.; Szliska C.
Universitats-Hautklinik, Schittenhelmstrasse 7,D 24105 Kiel Germany
Journal of the American Academy of Dermatology (J. AM. ACAD. DERMATOL.) (United States) 1994, 31/4 (584-591)
CODEN: JAADD ISSN: 0190-9622
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...patients with a standardized protocol. Results: Patch test efficiency was good (>=0.94) with all 10 allergens. In contrast, nonreproducibility of patch tests was strongly *allergen* dependent, ranging from 0.2 for nickel sulfate to 0.6 for formaldehyde. The likelihood of nonreproducible *allergic* reactions increased when more than four positive reactions were seen at the same time, and with another positive reaction located in close proximity to an *allergic* reaction. Sex and age of patients, atopy, dermatitis at distant sites, sleeping habits, and the time of *allergen* exposure (24 or 48 hours) did not affect the rate of nonreproducible results. Conclusion: To increase patch test reproducibility, specific preparations of patch test allergens...
DRUG DESCRIPTORS:
**allergen*
balsam peru; cobalt chloride; dichromate potassium; formaldehyde; kathon *cg*; lanolin alcohol; nickel sulfate; thiomersal; tuberculin
MEDICAL DESCRIPTORS:
**allergy*--diagnosis--di; *patch test
allergic reaction--diagnosis--di; article; calculation; diagnostic accuracy; female; human; major clinical study; male; priority journal; reproducibility; skin test
...CAS REGISTRY NO.: 7646-79-9 (cobalt chloride); 7778-50-9 (dichromate potassium); 50-00-0 (formaldehyde); 55965-84-9 (kathon *cg*); 8027-33-6 (lanolin alcohol); 7786-81-4 (nickel sulfate); 54-64-8 (thiomersal); 92129-86-7 (tuberculin)

6/3,K/22 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

05824775 EMBASE No: 1994230976
Epidemiologic study of the contact dermatitis in the north of Caceres
EPIDEMIOLOGIA DE LA DERMATITIS DE CONTACTO EN EL NORTE DE LA PROVINCIA DE CACERES
Cosmes Martin P.M.; Garcia Ortiz J.C.
C/ Maria de Rojas, 1,10600 Plasencia, Caceres Spain
Revista Espanola de Alergologia e Inmunologia Clinica (REV. ESP. ALERGOL. INMUNOL. CLIN.) (Spain) 1994, 9/3 (135-140)
CODEN: REACE ISSN: 0214-1477
DOCUMENT TYPE: Journal; Article

LANGUAGE: SPANISH SUMMARY LANGUAGE: ENGLISH; SPANISH

...5.72%), mercaptobenzothiazole (4.80%), formaldehyde (3.84%), lanoloin alcohol (3.84%), quaternium 15 (2.88%), quinoline mix (2.88%), caine mix (1.92%), khaton *CG* (1.92%), parabenum (1.92%), thiomersal (1.92%), epoxy resin (0.96%), balsam of Peru (0.96%), p-tert-butyphenol formaldehyde resin (0.96%). In women the most sensitizing *antigen* was nickel sulfate (59.49%), followed by fragrance mix (13.92%), colophony (10.12%) and potassium dichromate (10.12%). The incidence in men was: potassium...
DRUG DESCRIPTORS:
*contact *allergen*
MEDICAL DESCRIPTORS:
*contact dermatitis--diagnosis--di; *contact dermatitis--epidemiology--ep; **allergy*

6/3,K/23 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

05612638 EMBASE No: 1994005934
Patch test sensitivity in old and new German Federal states/IVDK 1990/91 versus Saxony 1991
VERGLEICH EPIDERMALER ALLERGIEQUOTEN IN ALTEN UND NEUEN DEUTSCHEN BUNDESLANDERN. IVDK 1990/91 VERSUS SACHSEN 1991
Richter G.
Klinik fur Hautkrankheiten, Med. Akademie Carl Gustav Carus, Fetscherstr. 74,D-01307 Dresden Germany
Dermatosen in Beruf und Umwelt (DERMATOSEN BERUF UMWELT) (Germany) 1993, 41/6 (217-220)
CODEN: DBUMD ISSN: 0343-2432
DOCUMENT TYPE: Journal; Article
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH; GERMAN; FRENCH

...and formaldehyde, which can be explained by a very different history of exposition in the two regions. In further substances, e.g., cobalt, parabenes, Kathon *CG*, thiuram, mercury (II) chloride, terpentine, ethylenediamine, the divergences were lower but still significant, and lacked such a clear explanation. As similar differences are known between ...
DRUG DESCRIPTORS:
**allergen*; *formaldehyde; *neomycin
MEDICAL DESCRIPTORS:
*patch test; *skin *allergy*--epidemiology--ep; *skin *allergy*--diagnosis --di

6/3,K/24 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

05611512 EMBASE No: 1994011673
The management of perianal dermatitis
MANAGEMENT DER PERIANALDERMATITIS
Huszar A.; Eichmann A.
Dermatologische Klinik, Universitatsspital, Gloriastrasse 31,CH-8091 Zurich Switzerland
Therapiewoche Schweiz (THERAPIEWOCHE SCHWEIZ) (Germany) 1993, 9/12 (789-792)
CODEN: THSCE ISSN: 0256-6869
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN

DRUG DESCRIPTORS:
*contact *allergen*--drug toxicity--to; *kathon *cg*--drug toxicity--to
MEDICAL DESCRIPTORS:

*anus disease--etiology-[redacted]; *dermatitis--etiology--et; *[redacted]n *allergy* --etiology--et
CAS REGISTRY NO.: 55965-84-9 (kathon *cg*); 8007-00-9 (balsam peru); 1333-08-0...

6/3,K/25 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

05541357 EMBASE No: 1993309457
Spectrum of allergens in contact dermatitis in the central and upper hessian catchment area of the Department of Dermatology and Andrology at the University of Giessen
DAS ALLERGENSPEKTRUM BEI KONTAKTEKZEMEN IM MITTEL- UND OBERHESSISCHEN EINZUGSGEBIET DER UNIV-HAUTKLINIK GIESSEN 1975-1989
Grunder K.; Lenzen P.; Mayser P.
Univ.-Hautklinik, Gaffkystr. 14,D-35392 Giessen Germany
Aktuelle Dermatologie (AKTUEL. DERMATOL.) (Germany) 1993, 19/9-10 (269-280)
CODEN: AKDED ISSN: 0340-2541
DOCUMENT TYPE: Journal; Article
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH; GERMAN

...showed one positive reaction at least in the standard series; the average number of positive reactions per patient amounted to 2.01. The most frequent *allergen* was nickel sulphate (13.1%), followed by cobalt chloride (9.3%), potassium dichromate (8.6%), balsam of Peru (8.1%), wool alcohols (5.4%) and...

...Newer allergens were taken up since 1990. A retrospective evaluation from 1990 and 1991 gave, relative to fragrance mixture, a frequence of 7%, concerning Kathon *CG* a frequence of 3,6%. The female sex showed a clear preference for (in sequence): nickel sulphate, cobalt chloride, balsam of Peru, Wool wax alcohol and PPD. Androtropism was noticed with potassium dichromate. Throughout the entire period nickel and cobalt *allergy* increased continually, while *allergy* caused by chromate decreased. Essentially unchanged was balsam of Peru. Allergies caused by one substance existed in 21.7%, those caused by two substances in...

...Among the different professions the building trade showed the highest rate of sensitivity, followed by the rubber-industry, the hairdressers and the plastic industry. Nickel *allergy* occurred especially in the hairdressers-branch, the food industry and the medical and nursing professions and at home. Chromate-*allergy* dominated in the building trade, in the metal industry and, in respect of cobalt chloride, also in the baker's profession. Professions with the highest...

...and the prothesis-block and slightly reactive the drugs, lacquers, plastics, adhesives and rubber blocks. The baker's block was last. The group that was *allergic* to nickel had the lowest average age 30.4 +/- 14.1 years, followed by cobalt chloride (35.2 +/- 15.3 years) and formalin (36.1 +/- 14.9 years). The group that was *allergic* to the Parabens (PHB esters) had the highest average age: 59.4 +/- 15.9 years. Middle-age groups are preferably *allergic* to potassium dichromate (42.0 +/- 14.4 years) and tetramethylthiuram disulfide (42.9 +/- 16.1 years).
DRUG DESCRIPTORS:
**allergen*--drug toxicity--to; **allergen*--adverse drug reaction--ae; *balsam peru--adverse drug reaction--ae; *balsam peru--drug toxicity--to; *cobalt chloride--drug toxicity--to; *cobalt chloride--adverse drug reaction--ae; *dichromate potassium--adverse drug reaction--ae; *dichromate potassium--drug toxicity--to; *formaldehyde--adverse drug reaction--ae; *formaldehyde--drug toxicity--to; *kathon *cg*--drug toxicity--to; *kathon *cg*--adverse drug reaction--ae; *lanolin--drug toxicity--to; *lanolin--adverse drug reaction--ae; *nickel sulfate--drug toxicity--to; *nickel sulfate--adverse drug reaction--ae; *tuberculin...

MEDICAL DESCRIPTORS:
**allergy*; *contact dermatitis; *patch test
...CAS REGISTRY NO.: 7646-79-9 (cobalt chloride); 7778-50-9 (dichromate potassium); 50-00-0 (formaldehyde); 55965-84-9 (kathon *cg*); 70321-63-0...

6/3,K/26 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE

05506179 EMBASE No: 1993274278
Contact *allergy* to some medicaments
ALLERGIA DA CONTATTO DA MEDICAMENTI PER USO TOPICO
Cusano F.; Capozzi M.; Adamo F.; Errico G.
Presidio Ospedaliero Multizonale, 'G. Rummo', Divisione di Dermatologia, Via dell'Angelo 1,82100 Benevento Italy
Annali Italiani di Dermatologia Clinica e Sperimentale (ANN. ITAL. DERMATOL. CLIN. SPER.) (Italy) 1993, 47/3 (189-193)
CODEN: ADCRA ISSN: 0365-169X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ITALIAN SUMMARY LANGUAGE: ITALIAN; ENGLISH

Contact *allergy* to some medicaments

The authors review the main aetiological and clinical features of *allergic* contact dermatitis due to topical drugs according to their recent experience. This pathology is commonly observed as often today as in the past, although old...

...that this chemical is now less frequently observed as a sensitizer than in the past. In contrast, we recorded 16 cases of contact and photocontact *allergic* dermatitis from topical antirheumatic drugs (1.6%); in particular, nonsteroidal anti-inflammatory medicaments represent a grossly increasing problem. Ketoprofen, an aryl-propionic acid derivative, was responsible for 8 cases of contact *allergy* in 1992 (4.3%), so that it was considered the major *allergen* for this year, after nickel and cobalt. Among antifungals, quinolines are still the most frequent sensitizers. No case of *allergy* due to imidazole derivatives was recorded, although they are widely used. In spite of few reports in the literature, *allergic* contact dermatitis to benzoyl peroxide in acne patients were infrequent albeit not rare. Among preservatives and surfactants, thiomersal heads the list of allergens. No reaction...

...5% (pet). Two patients (1.1%) strongly reacted to all the tests. As a comparison, in the same period we recorded 2 reactions to Kathon *CG*, and 4 to Euxyl K 400 and to cocamidopropyl betaine (2%). The last two haptens might represent an emerging problem in Italy.
DRUG DESCRIPTORS:
...reaction--ae; dexchlorpheniramine--adverse drug reaction--ae; euxyl k 400--adverse drug reaction--ae; feprazone--adverse drug reaction--ae; gentamicin--adverse drug reaction--ae; kathon *cg*--adverse drug reaction --ae; lanolin--adverse drug reaction--ae; neomycin--adverse drug reaction --ae; pilocarpine--adverse drug reaction--ae; piroxicam--adverse drug reaction--ae; propylene...
MEDICAL DESCRIPTORS:
*contact *allergy*
...CAS REGISTRY NO.: 1405-41-0 (gentamicin); 55965-84-9 (kathon *cg*); 70321-63-0...

6/3,K/27 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

05447988 EMBASE No: 1993216087

Alterations in the cutaneous immune response following topical applications of sodium lauryl sulfate and Kathon *CG*

Rheins L.A.; Haren M.A.; Buehler E.V.
Advanced Tissue Systems, 10933 N. Torrey Pines Road,La Jolla, CA 92037 United States
Journal of Toxicology - Cutaneous and Ocular Toxicology (J. TOXICOL. CUTANEOUS OCUL. TOXICOL.) (United States) 1993, 12/3 (249-259)
CODEN: JTOTD ISSN: 0731-3829
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Alterations in the cutaneous immune response following topical applications of sodium lauryl sulfate and Kathon *CG*

...the contact hypersensitivity (CHS) response. The current experiments demonstrated that topical application of a known irritant, sodium lauryl sulfate (SLS), and the purported sensitizer, Kathon *CG*, can in 5 days significantly increase the intensity of CHS reactions to 2.4-dinitro-1-fluorobenzene (DNFB) as measured using the ear thickness assay. There was a significant decrease in both immune Iasup + phenotypic and nonimmune ATPasesup + histochemical cell membrane markers following the SLS treatment. Topical Kathon *CG* caused a directional decrease in Iasup + and ATPasesup + epidermal cells. The use of rapid immunohistochemistry assays is discussed as screening methods after exposure to cutaneous...
DRUG DESCRIPTORS:
*dodecyl sulfate sodium--drug toxicity--to; *kathon *cg*--drug toxicity--to
1 fluoro 2,4 dinitrobenzene--drug toxicity--to; Ia *antigen*--endogenous compound--ec; adenosine triphosphatase--endogenous compound--ec
MEDICAL DESCRIPTORS:
*contact *allergy*--etiology--et
CAS REGISTRY NO.: 151-21-3 (dodecyl sulfate sodium); 55965-84-9 (kathon *cg*); 25376-51-6...

6/3,K/28 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE

05072772 EMBASE No: 1992212988
Contact *allergy* to Kathon: Elimination or declaration?
KONTAKTALLERGIE AUF KATHON: ELIMINATION ODER DEKLARATION?
Aberer W.; Ziegler V.; Anegg B.
I. Universitats-Hautklinik, Alserstrasse 4,A-1090 Wien Austria
Dermatosen in Beruf und Umwelt (DERMATOSEN BERUF UMWELT) (Germany) 1992, 40/3 (112-115)
CODEN: DBUMD ISSN: 0343-2432
DOCUMENT TYPE: Journal; Article
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN; ENGLISH; FRENCH

Contact *allergy* to Kathon: Elimination or declaration?

...probably released a flood of publications, both in the scientific literature and in the lay press in such a short time as the preservative Kathon *CG*. Patch test results in eczema patients have revealed sensitization rates ranging from 0.67 up to 16.1%, the problem of too high concentrations in...

...in 'Contact Dermatitis' dating from 1985 to 1990 and dedicated primarily to the Kathon-problem, based their conclusions on conventional patch test results alone. Kathon *CG* is definitely a potential *antigen*, but whether it is - upon correct application - a potent *allergen* remains yet to be elucidated.
BRAND NAME/MANUFACTURER NAME: kathon *cg*/roehm pharma/United States
DRUG DESCRIPTORS:
*antiinfective agent; *kathon *cg*--adverse drug reaction--ae
MEDICAL DESCRIPTORS:

*contact *allergy*--diagnosis--di; *contact *allergy*--etiology--et; *
eczema--diagnosis--di; *eczema--etiology--et; *skin *allergy*--diagnosis
--di; *skin *allergy*--etiology--et
CAS REGISTRY NO.: 55965-84-9 (kathon *cg*)

6/3,K/29 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE

05029848 EMBASE No: 1992170064
A multicentre study of contact sensitization in children
Ayala F.; Balato N.; Lembo G.; Patruno C.; Tosti A.; Schena D.; Pigatto
P.; Angelini G.; Lisi P.; Rafanelli A.
Cattedra di Dermatologia, Policlinico Mater Domini, Via T
Campanella,88100 Catanzaro Italy
Contact Dermatitis (CONTACT DERMATITIS) (Denmark) 1992, 26/5 (307-310)
CODEN: CODED ISSN: 0105-1873
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

DRUG DESCRIPTORS:
**allergen*--drug toxicity--to
drug--adverse drug reaction--ae; kathon *cg*--drug toxicity--to; mercury
--drug toxicity--to; metal--drug toxicity--to; neomycin--adverse drug
reaction--ae; nickel--drug toxicity--to; perfume--drug toxicity--to;
preservative...
MEDICAL DESCRIPTORS:
*childhood disease--epidemiology--ep; *childhood disease--side effect--si;
*childhood disease--etiology--et; *childhood disease--diagnosis--di; *
contact sensitization; *patch test; *skin *allergy*--diagnosis--di; *skin
allergy--side effect--si; *skin *allergy*--etiology--et; *skin *allergy*
--epidemiology--ep
CAS REGISTRY NO.: 55965-84-9 (kathon *cg*); 14302-87-5...

6/3,K/30 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE

04983403 EMBASE No: 1992123619
The 'Isothiazolinone story'
Hunziker N.
Department of Dermatology, Hospital Cantonal Universitair,CH-1211 Geneva
4 Switzerland
Dermatology (DERMATOLOGY) (Switzerland) 1992, 184/2 (85-86)
CODEN: DERAE ISSN: 1018-8665
DOCUMENT TYPE: Journal; Editorial
LANGUAGE: ENGLISH

DRUG DESCRIPTORS:
*isothiazole derivative--adverse drug reaction--ae; *kathon *cg*--adverse
drug reaction--ae; *preservative
allergen; cosmetic; unclassified drug
MEDICAL DESCRIPTORS:
*contact *allergy*--etiology--et; *contact *allergy*--side effect--si; *
contact dermatitis--etiology--et; *contact dermatitis--side effect--si
CAS REGISTRY NO.: 55965-84-9 (kathon *cg*); 1003-07-2 (isothiazolone)

6/3,K/31 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

04916514 EMBASE No: 1992056730
***Allergic* contact dermatitis and vulvar dermatoses**

Marren P.; Wojnarowska [redacted]; Powell S.
Department of Dermatology, Slade Hospital,Headington, Oxford OX3 7JH United Kingdom
British Journal of Dermatology (BR. J. DERMATOL.) (United Kingdom) 1992, 126/1 (52-56)
CODEN: BJDEA ISSN: 0007-0963
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

***Allergic* contact dermatitis and vulvar dermatoses**

...therapy can be unsatisfactory. There is some evidence that vulvar sensitivity to irritants is higher than that of forearm skin, but the incidence of relevant *allergic* contact sensitivity amongst this patient population is unknown. The patch-test data over a 5-year period of 135 patients with persistent vulval symptoms were...
DRUG DESCRIPTORS:
**allergen*--adverse drug reaction--ae; *antibiotic agent--adverse drug reaction--ae; *cosmetic--adverse drug reaction--ae; *preservative--adverse drug reaction--ae
...drug reaction--ae; hydrocortisone--adverse drug reaction--ae; hydrocortisone--drug combination--cb; hydrocortisone butyrate--adverse drug reaction--ae; hydrogen peroxide--adverse drug reaction--ae; kathon *cg* --adverse drug reaction--ae; lanolin alcohol--adverse drug reaction--ae; lidocaine; mercaptobenzothiazole--adverse drug reaction--ae; neomycin --adverse drug reaction--ae; nickel sulfate--adverse drug...
...CAS REGISTRY NO.: 51260-59-4 (hexadecanol); 50-23-7 (hydrocortisone); 13609-67-1 (hydrocortisone butyrate); 7722-84-1 (hydrogen peroxide); 55965-84-9 (kathon *cg*); 8027-33-6 (lanolin alcohol); 137-58-6...

6/3,K/32 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE

04891118 EMBASE No: 1992031333
Contact *allergic* dermatitis to an electrocardiography
DERMATITIS ALERGICA DE CONTACTO AL GEL DE ELECTROCARDIOGRAFIA
Aniz E.; De La Cuadra J.; De Mateo A.; Aliaga A.
Servicio de Dermatologia, Hospital General Universitario de Valencia, Avda. Tres Cruces, s/n, Valencia Spain
Medicina Cutanea Ibero-Latino-Americana (MED. CUTANEA IBERO-LAT.-AM.) (Spain) 1991, 19/6 (317-319)
CODEN: MCILB ISSN: 0210-5187
DOCUMENT TYPE: Journal; Article
LANGUAGE: SPANISH SUMMARY LANGUAGE: ENGLISH; SPANISH

Contact *allergic* dermatitis to an electrocardiography
DRUG DESCRIPTORS:
2 propanol--adverse drug reaction--ae; 4 hydroxybenzoic acid ester--adverse drug reaction--ae; alcohol--adverse drug reaction--ae; *allergen*--adverse drug reaction--ae; carbomer--pharmaceutics--pr; chloroxylenol--adverse drug reaction--ae; clioquinol--adverse drug reaction--ae; geraniol--adverse drug reaction--ae; kathon *cg*--pharmaceutics--pr; lanolin--adverse drug reaction--ae; mercaptobenzothiazole--adverse drug reaction--ae; neomycin --adverse drug reaction--ae; nickel--adverse drug reaction--ae; perfume --adverse drug...
...CAS REGISTRY NO.: 8057-20-3 (clioquinol); 106-24-1 (geraniol); 55965-84-9 (kathon *cg*); 70321-63-0...

6/3,K/33 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE

04861707 EMBASE No: 1992001922

Merbromin in contact dermatitis
MERBROMINA EN DERMATITIS DE CONTACTO
Romaguera Sagrera C.; Zemba C.; Mascaro J.M.
Servicio de Alergie, Departamento de Dermatologia, Hospital Clinic y Provincial, Barcelona Spain
Medicina Cutanea Ibero-Latino-Americana (MED. CUTANEA IBERO-LAT.-AM.) (Spain) 1991, 19/4 (227-231)
CODEN: MCILB ISSN: 0210-5187
DOCUMENT TYPE: Journal; Article
LANGUAGE: SPANISH SUMMARY LANGUAGE: SPANISH; ENGLISH

DRUG DESCRIPTORS:
**allergen*--pharmacology--pd; *merbromin--pharmacology--pd
...cobalt chloride--pharmacology--pd; cobalt sulfate--pharmacology--pd; detergent--pharmacology--pd; dichromate potassium--pharmacology--pd; ethylenediamine--pharmacology--pd; formaldehyde--pharmacology--pd; hexachlorophene--pharmacology--pd; kathon *cg*--pharmacology--pd; lanolin alcohol--pharmacology--pd; mercaptobenzothiazole--pharmacology--pd; mercury --pharmacology--pd; mercury chloride--pharmacology--pd; mercury derivative --pharmacology--pd; neomycin--pharmacology--pd; nickel sulfate...
MEDICAL DESCRIPTORS:
*contact dermatitis; *skin *allergy*; *skin test
...CAS REGISTRY NO.: 70-30-4 (hexachlorophene); 55965-84-9 (kathon *cg*); 8027-33-6 (lanolin alcohol); 27157-85-3 (mercaptobenzothiazole); 14302-87-5...

6/3,K/34 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

04754119 EMBASE No: 1991247473
Isothiazolinones (MCI/MI): 200 ppm versus 100 ppm in the standard series
Farm G.; Wahlberg J.E.
Department of Occupational, Dermatology, Karolinska Hospital,S-104 01 Stockholm Sweden
Contact Dermatitis (CONTACT DERMATITIS) (Denmark) 1991, 25/2 (104-107)
CODEN: CODED ISSN: 0105-1873
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...9 had reactions of the same strength. Use tests were carried out in 7 cases, of which 2 were positive. MCI/MI remains a peculiar *allergen* and some of the problematic factors are: the morphology of the test reactions, the difficulties in tracking down the exposure (past or current relevance), the...
DRUG DESCRIPTORS:
*2 methyl 4 isothiazolin 3 one--adverse drug reaction--ae; *5 chloro 2 methyl 4 isothiazolin 3 one--adverse drug reaction--ae; *kathon *cg* --adverse drug reaction--ae; *preservative--adverse drug reaction--ae
MEDICAL DESCRIPTORS:
*skin *allergy*--side effect--si
CAS REGISTRY NO.: 2682-20-4 (2 methyl 4 isothiazolin 3 one); 26172-55-4 (5 chloro 2 methyl 4 isothiazolin 3 one); 55965-84-9 (kathon *cg*)

6/3,K/35 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE

04667125 EMBASE No: 1991161170
Contact allergies to new preservatives
KONTAKTALLERGIEN GEGEN NEUERE KONSERVIERUNGSMITTEL
Senff H.; Kollner A.; Tholen S.; Frosch P.J.
Klinik fur Dermatologie und Allergologie, St. Barbara-Hospital, Barbarastrasse 67, W-4100 Duisburg 11 Germany

Hautarzt (HAUTARZT) (Germany) 1991, 42/4 (215-219)
CODEN: HAUTA ISSN: 0017-8470
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH

...pharmaceutical industry is searching for alternatives that will be effective, safe and economical. The present paper introduces a selection of new or revived biocides (Kathon *CG*, benzisothiazolinone, Euxyl K 400, Biobans, Grotans, Bronopol, Germall II), and the range of application and the sensitization potency of each are discussed. Test concentrations for patch tests are recommended. Kathon *CG* is the most commonly used preservative among these biocides, although it has a high sensitization potency and is a frequently encountered contact *allergen*. To make discovery of a new *allergen* easier and to reduce the risk of side effects, manufacturers should be required to specify the ingredients of their products on the labels.
BRAND NAME/MANUFACTURER NAME: kathon *cg*; euxyl k 400; bioban; grotan; germall ii
DRUG DESCRIPTORS:
*bronopol--adverse drug reaction--ae; *euxyl k 400--adverse drug reaction --ae; *isothiazole derivative--adverse drug reaction--ae; *kathon *cg* --adverse drug reaction--ae
MEDICAL DESCRIPTORS:
*contact *allergy*--diagnosis--di; *contact *allergy*--etiology--et; * contact *allergy*--side effect--si
CAS REGISTRY NO.: 52-51-7 (bronopol); 98668-04-3 (euxyl k 400); 55965-84-9 (kathon *cg*); 78491-02-8 (diazolidinyl urea)

6/3,K/36 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE

04604445 EMBASE No: 1991098488
Contact dermatitis
Romaguera C.; Grimalt F.
Monografias de Dermatologia (MONOGR. DERMATOL.) (Spain) 1990, 3/6 (362-368)
CODEN: MONDE ISSN: 0214-4220
DOCUMENT TYPE: Journal; Article
LANGUAGE: SPANISH SUMMARY LANGUAGE: ENGLISH

DRUG DESCRIPTORS:
**allergen*--pharmacology--pd
...pharmacology--pd; cobalt chloride--pharmacology--pd; dichromate potassium--pharmacology--pd; epoxy resin--pharmacology--pd; ethylenediamine --pharmacology--pd; formaldehyde--pharmacology--pd; guanidine derivative --pharmacology--pd; kathon *cg*--pharmacology--pd; lanolin--pharmacology --pd; local anesthetic agent--pharmacology--pd; mercury--pharmacology--pd; naphthyl group--pharmacology--pd; neomycin--pharmacology--pd; nickel sulfate--pharmacology--pd; perfume...
MEDICAL DESCRIPTORS:
*contact *allergy*--diagnosis--di; *contact *allergy*--etiology--et; * contact dermatitis--diagnosis--di; *contact dermatitis--etiology--et; * eczema; *patch test; *skin test
...CAS REGISTRY NO.: 7646-79-9 (cobalt chloride); 7778-50-9 (dichromate potassium); 107-15-3 (ethylenediamine); 50-00-0 (formaldehyde); 55965-84-9 (kathon *cg*); 70321-63-0...

6/3,K/37 (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE

04599593 EMBASE No: 1991093636
Epidemiological survey of standard series patch test results and

observations on day 2 and day 4 readings
Shehade S.A.; Beck M.H.; Hillier V.F.
Skin Hospital, Salford M60 9EP United Kingdom
Contact Dermatitis (CONTACT DERMATITIS) (Denmark) 1991, 24/2 (119-122)
CODEN: CODED ISSN: 0105-1873
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Computer data on 4721 consecutive patients patch tested with an extended standard series were analysed for the frequency of *allergic* reactions to each substance. Particular attention was given to the negative first reading at day 2 (D2) which later became positive at day 4 (D4). A total of 4210 *allergic* reactions were recorded, 993 of which were negative on D2 (24%). The most frequent positive reactions were to nickel sulphate (18%), fragrance-mix (8%), colophony...
DRUG DESCRIPTORS:
**allergen*--adverse drug reaction--ae; **allergen*--drug toxicity--to; * cobalt chloride--drug toxicity--to; *dichromate potassium--drug toxicity --to; *disulfiram--drug toxicity--to; *neomycin--adverse drug reaction--ae; *neomycin--drug toxicity...
...epoxy resin--adverse drug reaction--ae; ethylenediamine--adverse drug reaction--ae; ethylenediamine--drug toxicity--to; formaldehyde--adverse drug reaction--ae; formaldehyde--drug toxicity--to; kathon *cg*--adverse drug reaction--ae; kathon *cg*--drug toxicity--to; propylene glycol --adverse drug reaction--ae; propylene glycol--drug toxicity--to; quinoline --adverse drug reaction--ae; quinoline--drug toxicity--to; sorbic acid...
MEDICAL DESCRIPTORS:
*patch test; *skin *allergy*--side effect--si
...CAS REGISTRY NO.: 8039-39-2 (dimethylcarbamic acid 1 isopropyl 3 methylpyrazol 5 yl ester); 107-15-3 (ethylenediamine); 50-00-0 (formaldehyde); 55965-84-9 (kathon *cg*); 57-55-6 (propylene glycol); 91-22-5 (quinoline); 110-44-1...

6/3,K/38 (Item 21 from file: 73)
DIALOG(R)File 73:EMBASE

03650046 EMBASE No: 1988099482
Ring-shaped positive *allergic* patch test reactions to allergens in liquid vehicles
Lachapelle J.M.; Tennstedt D.; Fyad A.; Masmoudi M.L.; Nouaigui H.
Unit of Occupational Dermatology, Louvain University, 1200 Brussels Belgium
Contact Dermatitis (CONTACT DERMATITIS) (Denmark) 1988, 18/4 (234-236)
CODEN: CODED ISSN: 0105-1873
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Ring-shaped positive *allergic* patch test reactions to allergens in liquid vehicles

In recent years, we have observed several 'ring-shaped' positive *allergic* patch test reactions to allergens dissolved in a liquid vehicle, a more intense response at the periphery of the site of application than in the central part. The occurrence of such reactions was evaluated for fomaldehyde, Kathon *CG*, hydrocortisone and hexamidine diisethionate. Possible explanations for such reactions include pressure and/or a capillary effect.
DRUG DESCRIPTORS:
**allergen*; *formaldehyde; *hexamidine isetionate; *hydrocortisone

6/3,K/39 (Item 22 from file: 73)
DIALOG(R)File 73:EMBASE

2/3,K/4
DIALOG(R)File 155:MEDLINE(R)

07837253 93367247 PMID: 8360497

Induction of antibodies to a kappa V region by gene immunization.

Watanabe A; Raz E; Kohsaka H; Tighe H; Baird S M; Kipps T J; Carson D A
Department of Medicine, University of California, San Diego, La Jolla 92093-0663.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Sep 1 1993, 151 (5) p2871-6, ISSN 0022-1767 Journal Code: 2985117R
Contract/Grant No.: AR25443; AR; NIAMS; AR41897; AR; NIAMS; CA57868; CA; NCI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... in V regions of several human IgM autoantibodies and is used frequently in chronic lymphocytic leukemia. This gene was inserted into a mammalian expression vector, *pREP7*, to produce pREVk3. Mice injected i.m. with pREVk3 produced antibodies against the V region of Glo, a human monoclonal IgM paraprotein whose kappa L...
?ds

Set	Items	Description
S1	0	(PREP7) (S) (INVITROGEN)
S2	4	(PREP7)

?logoff
19feb03 11:53:59 User259876 Session D467.2
$0.98 0.305 DialUnits File155
$0.84 4 Type(s) in Format 3
$0.84 4 Types
$1.82 Estimated cost File155
$0.70 TELNET
$2.52 Estimated cost this search
$2.81 Estimated total session cost 0.386 DialUnits

Status: Signed Off. (3 minutes)

```
### Status: Path 1 of [Dialog Information Services via Modem]

### Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
### Status: Signing onto Dialog
 ********
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
### Status: Connected


Dialog level 02.12.60D

Last logoff:  19feb03 11:46:15
Logon file001 19feb03 11:51:23
KWIC is set to 50.
HILIGHT set on as '*'
* *  New CURRENT Year ranges installed    **

File   1:ERIC  1966-2003/Jan 22
       (c) format only 2003 The Dialog Corporation

      Set  Items  Description
      ---  -----  -----------
Cost is in DialUnits
?b 155
       19feb03 11:51:27 User259876 Session D467.1
            $0.28    0.081 DialUnits File1
     $0.28  Estimated cost File1
     $0.01  TELNET
     $0.29  Estimated cost this search
     $0.29  Estimated total session cost   0.081 DialUnits


File 155:MEDLINE(R)  1966-2003/Feb W2
       (c) format only 2003 The Dialog Corp.

      Set  Items  Description
      ---  -----  -----------
?s (pREP7) (s) (invitrogen)
               4  PREP7
              23  INVITROGEN
      S1       0  (PREP7) (S) (INVITROGEN)
?s (pREP7)
      S2       4  (PREP7)
?t s2/3,k/all

 2/3,K/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

10856662   20399864   PMID: 10945767
  Nonviral glial cell-derived neurotrophic factor gene transfer enhances
survival of cultured dopaminergic neurons and improves their function after
transplantation in a rat model of Parkinson's disease.
  Bauer M; Meyer M; Grimm L; Meitinger T; Zimmer J; Gasser T; Ueffing M;
Widmer H R
  Department of Neurology, Klinikum Grosshadern, Ludwig Maximilians
Universitat Munchen, Munich, Germany.
  Human gene therapy (UNITED STATES)  Jul 20 2000,  11  (11)  p1529-41,
```

ISSN 1043-0342 Journal Code: 9008950
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... organotypic free-floating roller tube (FFRT) cultures with a vector encoding human glial cell-derived neurotrophic factor (hGDNF). For transfer of an episomal expression vector (*pRep7*-GDNF8) a nonviral, nonliposomal cationic transfection technique was applied and optimized. Recombinant hGDNF expression resulted in a higher number of TH-positive neurons in the ...

2/3,K/2
DIALOG(R)File 155:MEDLINE(R)

10031792 99035167 PMID: 9816319
Prostate-specific membrane antigen: a novel folate hydrolase in human prostatic carcinoma cells.
Pinto J T; Suffoletto B P; Berzin T M; Qiao C H; Lin S; Tong W P; May F; Mukherjee B; Heston W D
Nutrition Research Laboratory, Urology Research Laboratory, Pharmacology Analytical Laboratory, and George M. O'Brien Urology Research Center, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Sep 1996, 2 (9) p1445-51, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA 08748-29; CA; NCI; CA 39203; CA; NCI; DK/CA 47650; DK; NIDDK; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... they react with 7E11-C5 monoclonal antibody. After transfection of PC-3 cells with a full-length 2.65-kb PSM cDNA subcloned into a *pREP7* eukaryotic expression vector, non-PSM antigen-expressing PC-3 cells developed immunoreactivity to 7E11-C5 monoclonal antibody and demonstrated folate hydrolase activities and optimum pH...

2/3,K/3
DIALOG(R)File 155:MEDLINE(R)

08729127 96077143 PMID: 7492311
Synthesis of a Cys949Tyr alpha 2-macroglobulin thiol ester mutant: co-transfection with wild-type alpha 2-macroglobulin in an episomal expression system.
Van Rompaey L; Van den Berghe H; Marynen P
Center for Human Genetics-Flanders Interuniversity Institute for Biotechnology, University of Leuven, Belgium.
Biochemical journal (ENGLAND) Nov 15 1995, 312 (Pt 1) p183-90, ISSN 0264-6021 Journal Code: 2984726R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

A full-length alpha 2-macroglobulin (alpha 2M) cDNA was cloned into the episomal expression vectors *pREP7* and pMEP4. Electroporation of the cell lines WI-L2-729HF2, U-937, K-562 and an Epstein-Barr virus-transformed cell line resulted in stable...

Office Action Summary	Application No.	Applicant(s)	
	09/265,191	CARSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *262-266* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *262-266* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 5/9/2002 in Paper No. 35 has been entered.

Applicants' request for interference between the present application and U.S. Patent Nos. 6,207,646 and 6,194,388, in Paper No. 36 is held in abeyance until the pending claims are in conditions for allowance.

Claims 202-204 and newly added claims 205-206 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Priority

The present application is a continuation of U.S. Serial No. 08/593554, filed January 30, 1996, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/446,691, filed June 7, 1995, now abandoned, which is a 371 national phase filing of PCT/US94/09661, filed August 25, 1994, which designated the U.S., which is a continuation-in-part of U.S. Serial No. 08/112,440, filed August 26, 1993.

Upon review of the specifications of great-grandparent (U.S Serial No. 08/112,440), grandparent (U.S. Serial No. 08/446,691) and parent (U.S. Serial No. 08/593,554) applications and comparison with the specification of the present application, it is determined that the pending claims are only entitled to the priority benefit of the filing date of January 30, 1996. When read in light of the present specification, claims 202 and 203 encompass a composition comprising a recombinant

antigen and any plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and wherein the immunostimulatory nucleic acid sequence is either already present in the plasmid or it is inserted into the plasmid in any desired copy numbers, including the plasmid pREP7 (see instant specification, page 11, second full paragraph, last paragraph continues to first paragraph on page 12), and that said antigen is produced by a process using the plasmid. Similarly, claims 204-205 encompass methods of treating an allergy in a vertebrate or an allergic response to an antigen in a mammal utilizing an effective amount of an immunostimulatory nucleic acid comprising the 5'CG3' motif in any plasmid, wherein C is unmethylated, and wherein the immunostimulatory nucleic acid is either already present in the plasmid or it is inserted into the plasmid in any desired copy numbers and an effective amount of a recombinant antigen that is produced by a process using the plasmid. The embodiments of these instant claims, claims 202-205, are not supported by the specifications of the great-grandparent application U.S. Serial No. 08/112,440, filed August 26, 1993 and the grandparent application U.S. Serial No. 08/446,691, filed June 7, 1995. There is no explicit teachings regarding to any immunostimulatory nucleic acid sequence, let alone an immunostimulatory nucleic acid comprising 5'CG3' or one comprising AACGTT in the aforementioned great-grandparent and grandparent applications. The mere mentioning that "Other preferred plasmid vectors are pREP7 and pREV which are commercially available from Invitrogen of San Diego, California" (page 23, lines 17-18 in U.S. Serial No. 08/112,440; page 33, lines 1-2, in U.S. Serial No. 08/446,691) is not an indication that at the filing dates of the great-

grandparent and grandparent applications, Applicants appreciate or realize the potential usefulness of any immunostimulatory nucleic acid sequence comprising the CpG motif, wherein C is unmethylated, as an adjuvant to stimulate CTL activity or to stimulate production of interferons by lymphocytes as contemplated by the present application (page 10, first paragraph of the present specification). As such, on the basis of the aforementioned great-grandparent and grandparent applications, it is not apparent to one of ordinary skilled artisan that Applicants contemplated specifically to make and use a composition comprising a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' or introducing said immunostimulatory nucleic sequence into any plasmid that is absent of such immunostimulatory nucleic acid sequence at any time period prior to January 30, 1996. Furthermore, there is also no support in the grandparent or the great-grandparent applications for the make and use of any plasmid containing an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' in conjunction or in a combination with an antigen in any form.

Accordingly, claims 202-205 are only entitled to the priority benefit of the filing date of January 30, 1996 for the reasons set forth above.

Claim 206 is entitled to the priority benefit of the filing date 8/26/1993.

Response to Arguments

Applicants' argument related to the priority of the claims in the Amendment filed on May 09, 2002 in Paper No. 35 (pages 4-5) have been fully considered.

With respect to claims 202-203, Applicants argued that Applicants are entitled to priority benefit of the filing date of U.S. Serial No. 08/112,440, filed August 26, 1993, because the great-grandparent application has the support for the instant claims by referring to Example 1, pages 32-33 regarding on the construction of the plasmid pREVk3. Examiner respectfully finds Applicants' argument to be unpersuasive for the following reasons.

While example 1 discloses the construction of an antigen-expressing vector, pREVk3, based on pREP7, there is no explicit teachings regarding to the make and use of any immunostimulatory nucleic acid sequence, let alone an immunostimulatory nucleic acid comprising 5'CG3' or one comprising AACGTT in the great-grandparent application. It is apparent that on the basis of the great-grandparent's disclosure that Applicants did not appreciate or realize the potential usefulness of any immunostimulatory nucleic acid sequence comprising the CpG motif, wherein C is unmethylated, as an adjuvant to stimulate CTL activity or to stimulate production of interferons by lymphocytes as contemplated by the present application (page 10, first paragraph of the present specification). It is also apparent to one of ordinary skilled artisan that Applicants did not contemplate specifically to make and use a composition comprising a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' or introducing said immunostimulatory nucleic sequence into any

plasmid that is absent of such immunostimulatory nucleic acid sequence at any time period prior to January 30, 1996. The disclosure that the plasmid vector pREP 7 contains an ampicillin resistance gene, which in turn contains the immunostimulatory sequence AACGTT is only made after the filing date of the great-grandparent application. Moreover, it is also apparent to one of ordinary skilled artisan that Applicants did not contemplate to make and use of any plasmid containing an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' in conjunction or in a combination with an antigen in any form as a two component system (a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT and an antigen as separate components) at any time period prior to January 30, 1996, because there is no support for such teachings in the great-grandparent applications. The disclosure for the preparation of the plasmid pREVk3 encoding an antigen (a single component system) does not support for this embodiment of the instant claims.

Accordingly, claims 202-205 are only entitled to the priority benefit of the filing date of January 30, 1996 for the reasons set forth above.

Claim Rejections - 35 USC § 112

Claim 204 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for suppressing an allergic response to an antigen in a mammal susceptible to an allergic reaction to said antigen which stimulates production of allergy-associated IgE antibodies in the mammal, comprising parenterally administering to the mammal (a) an effective amount of an

immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and (b) an effective amount of the antigen, does not reasonably provide enablement for other embodiments of the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

In light of the as-filed specification, the claim as written is directed to a method of treating an allergy in any vertebrate (e.g., frog, chicken, fish, mammal) comprising administering to the vertebrate an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and an effective amount of a recombinant antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is produced by a process using the plasmid.

With respect to the nature of the instant claim, the specification teaches by exemplification showing that mice that received intradermally the pCMV-lacZ vector containing two copies of the immunostimulatory polynucleotide with the sequence

AACGTT within the AmpR gene of the vector produced high titers of IgG 2A antibodies (serological markers for a TH1 type immune response), whereas mice injected intradermally with β-galactosidase produced high titers of IgG 1 antibodies (serological markers for a TH2 type immune response). The same groups of mice were boosted with 0.5 μg of β-galactosidase intradermally, boosting intradermal pCMV-lacZ primed mice with the enzyme induced about 10-fold rise in IgG 2A antibody responses, whereas it did not stimulate an IgG 1 response. It is noted that boosting intradermal β-galactosidase primed mice with the enzyme induced a significant rise in IgG 1 responses without any stimulation of an IgG 2A response, and that boosting of intramuscular pCMV-lacZ primed mice with the enzyme has little induction in either IgG 2A or IgG 1 responses (See Figs. 15 and 16). The specification further teaches that upon an intraperitoneal challenge with β-galactosidase 14 weeks after the initial immunization, anti-β-galactosidase IgE levels in intradermal pCMV-lacZ mice were consistently low after boosting as before boosting, while protein injected mice developed high levels of anti-β-galactosidase IgE, especially after the first antigen boosting injection (Fig. 17). Furthermore, Applicants teach that CTL activity in cultures of cells from the pCMV-lacZ injected mice increased from about 18% activity to nearly 100% activity, whereas the CTL activity in cell cultures from the pKCB-lacZ (without the immunostimulatory polynucleotide) or control injected mice barely exceeded 20% lytic activity. An increase in CTL activity was however observed in cell cultures from pKCB-lacZ & pUC-19 (pUC-19 plasmid vector includes the AmpR gene) co-injected mice.

The above evidence has been noted and considered. However, the above evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

The breadth of the instant claim encompasses a method for attaining a broad range of therapeutic effects ranging from reducing or alleviating to complete abolishment or preventing symptoms associated with an allergy in a vertebrate (within the scope of treating) comprising the utilization of an effective amount of an immunostimulatory nucleic acid comprising 5'CG3' in a plasmid of the presently claimed invention. The present specification is not enabled for such a broadly claimed invention. There is no reasonable correlation between an apparent lack of IgG 1 response stimulation and low levels of anti-β-galactosidase IgE levels observed in intradermal pCMV-lacZ primed mice after boosting with β-galactosidase with the prevention or abolishment of symptoms associated with any allergy in a vertebrate as encompassed by the scope of the instant claim. This is because after boosting with β-galactosidase, IgG 1 response was still present in the intradermal pCMV-lacZ primed mice, and although low levels of anti-β-galactosidase IgE were observed in the same mice, these levels are nevertheless represent a significant stimulation with respect to the pre-boosting anti-β-galactosidase IgE level (see Fig. 17). Moreover, splenocytes removed from pCMV-LacZ treated mice and challenged *in vitro* with β-galactosidase antigen are still capable of producing enhanced levels of IFN-γ and IL-4 in comparison with the splenocytes removed from the negative control pKCB-LacZ treated mice (see Example IX). The cytokine IL-4 is well known for turning on the IgE-producing cells and for

development of the TH2 cells. It is also not apparent from the instant specification that an effective mucosal immunity has been established or achieved in a vertebrate by the presently claimed invention since the mucosal immunity is important to prevent pathogen entry, for this instance allergens causing allergy to yield the prophylactic or preventive therapeutic effects contemplated by Applicants. Even several years after the effective filing date of the present application, the role of CpG immunostimulatory sequence in regulating host immune responses is still not clearly understood as exemplified by the teachings of McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). McCluskie et al. stated that "[I]t is possible that the CpG content of the vector may influence whether immune responses are biased towards a Th1- or Th2-type and explain, at least in part, why different plasmids induce predominantly Th1, Th2, or mixed Th1/Th2 responses when naked DNA is delivered to the lungs" (page 313, col. 2, first paragraph). McCluskie et al. further noted that various other factors such as the antigen, the dose of antigen, the route and method of DNA administration, the coexpression of cytokines and the presence or absence of other adjuvant may also involve in determining whether a Th1 or Th2 response predominates after mucosal immunization. As such, it is uncertain whether the scope of therapeutic effects contemplated by Applicants for the claimed method could be obtained by a skilled artisan without undue experimentation.

The instant claim also encompasses any route of delivering (encompassing parenteral and mucosal routes) an effective amount of an immunostimulatory nucleic acid of the present invention into a vertebrate to treat an allergy in said vertebrate. The

instant specification is not enabled for such a broadly claimed invention. This is because even among the parenteral routes of administration, boosting of intramuscular pCMV-lacZ primed mice with the enzyme does not enhance any IgG 2A response whose level is even lower than that induced in the β-galactosidase primed mice (See Fig. 15). Boosting intramuscular pCMV-lacZ primed mice with the enzyme also does not suppress the induction of IgG 1 response, but rather a slight stimulation was observed even though the stimulation level is much less than those obtained for intradermal pCMV-lacZ and β-galactosidase primed (See Fig. 16). Moreover, even in the absence of a subsequent boosting with the enzyme, the level of IgG 2A response to β-galactosidase is not stimulated upon intramuscular injection of pCMV-lacZ, whereas a significantly enhanced IgG 2A response was clearly observed for mice injected with β-galactosidase (see Fig. 13). Thus, it is apparent that there is a large variation in the selective induction of Th 1 response that is capable of providing the therapeutic effects contemplated by Applicants for treating an allergy between intramuscular and intradermal routes of administration, let alone any route of delivery. The instant specification offers no guidance for a skilled artisan on how to attain an induction of a desired Th1 immune response specific against an allergen via any mucosal route, given the unpredictable state of the art for attaining a desired induction of Th1 immune response that yields therapeutic effects through the introduction of CpG containing immunostimulatory sequences into mucosal surfaces as taught by McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). With the lack of sufficient guidance provided by the

present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

With respect to the breadth of the claim encompassing treating an allergy in a vertebrate including human, mouse, monkey, chicken, frog and fishes among others, the instant specification is not enabled for such a broadly claimed invention. Apart from the mouse model exemplification, it is unclear whether the desired selective induction of TH1 response that is beneficial for treating an allergy could be obtained in numerous species encompassed within the broad genus of a vertebrate in the claimed method. It is also unclear whether the immune components of a fish or a frog would react to an allergen in a similar manner as those of a mammal, and similarly whether an induction of the desired TH1 response would also be induced by the immunostimulatory nucleic acid of the presently claimed invention to yield the contemplated therapeutic effects. An extensive search for the prior art at the effective filing date of the present application revealed that little has been known about the immune responses in species such as frog, fish or chicken, let alone on the preferential induction in TH1 immune response for treating allergy in these species. As such, the contemplated therapeutic results for a broad number species encompassed by the scope of the present application would not be predictive. Thus, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed. Furthermore, regarding to the breadth for treating an allergy in any vertebrate in the method as claimed, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art and DNA vaccination, coupled with the breadth of the claim, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on May 09, 2002 in Paper No. 35 (pages 6-12) have been fully considered.

With respect to the issue of treating an allergy, Applicants argued that one of skilled in the art would understand that treating is directed to the goal of suppressing an allergic response and prevention or abolishment of allergy symptoms is not required. Applicants' argument is respectfully found unpersuasive. Since the term "treating" is not clearly defined in the specification, Examiner interprets the claim broadly to encompass prevention or abolishment of allergy symptoms within the scope of treating an allergy.

As such, the instant specification is not enabled for the full scope of treatment for the reasons set forth above. Should Applicants do not intend to claim treatment scopes including prevention or abolishment of allergy symptoms, then claim it appropriately.

With respect to the issue of route of administration, Applicants argued that the route of administration is not an element of the invention as long as effective amounts of the immunostimulatory nucleic acid and an antigen are introduced into the subject. Additionally, Applicants argued that that the apparent lack of a Th1 response in the animals receiving intramuscular administration in Figures 13-16 is just as likely due to the lesser amount of plasmid administered as due to the route of administration. Applicants' argument is respectfully found to be unpersuasive. This is because the route of administration is an important factor for determining an effective induction of a Th1 immune response to yield therapeutic effects contemplated by Applicants (e.g., suppression the production of allergy associated IgE antibodies) as evidenced by the teachings of McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). McCluskie et al. noted that various factors such as the antigen, the dose of antigen, the route and method of DNA administration, the coexpression of cytokines and the presence or absence of other adjuvant may also involve in determining whether a Th1 or Th2 response predominates after mucosal immunization. Even among two exemplified parenteral administration routes (intramuscular and intradermal), there is a large variation in the observed selective induction of Th 1 response that is capable of providing the therapeutic effects contemplated by Applicants for treating an allergy, let alone any route of delivery. With respect to Applicants' argument that the apparent

lack of a Th1 response in the animals receiving intramuscular administration in Figures 13-16 is just as likely due to the lesser amount of plasmid administered as due to the route of administration, there is no evidence of record supporting Applicants' assertion. Examiner noted that even with a 10 ug dosage, intradermal administration yields the expected induction of a specific Th1 immune response (10-fold rise in IgG2A antibody responses without a stimulation of IgG1 response) following boosting with the antigen. In contrast using the same dosage and the same vector construct, intramuscular administration had little induction of either IgG1 or IgG2A responses. Therefore, it is the route of administration and not the amount of plasmid administered seems to play an important role in the induction of a desired Th1 immune response. Furthermore, Applicants are invited to point out specifically the effective amounts of the immunostimulatory nucleic acid and an antigen being administered into any mucosal surfaces to elicit the desired Th1 immune response for treating an allergy in a vertebrate.

With respect to the issue of vertebrate, Applicants simply argued that the specification describes methods for stimulating a Th1 immune response and/or suppressing a Th2 immune response in a host such that an allergy is treated, therefore it is fully enabled for the method as claimed. Applicants' argument is respectfully found unpersuasive because apart from the mouse (a mammal) model exemplification, it is unclear whether the desired selective induction of TH1 response that is beneficial for treating an allergy could be obtained in numerous species encompassed within the broad genus of a vertebrate (fish, frog, reptiles among others) in the claimed method. It

is also unclear whether the immune components of a fish or a frog would react to an allergen in a similar manner as those of a mammal, and similarly whether an induction of the desired TH1 response would also be induced by the immunostimulatory nucleic acid of the presently claimed invention to yield the contemplated therapeutic effects. An extensive search for the prior art at the effective filing date of the present application revealed that little has been known about the immune responses in species such as frog, fish or chicken, let alone on the preferential induction in TH1 immune response for treating allergy in these species. With the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Applicants further stated that in order to maintain the rejection regarding to the breath of the claim on the issues of "route of administration" and "vertebrate", the rejection must have the approval of the Technology Center Director because the rejection would equally apply to claims of U.S. Patent No. 6,207,646. Examiner would like to state that the issued claims of U.S. Patent No. 6,207,646 are not relevant to the examination of the pending claims of this as-filed application, because each application is treated on its own merits and because the pending claims are still under examination and they are not in conditions for allowance for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 204 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 204, the phrase "an effective amount of an immunostimulatory nucleic acid in a plasmid,....., and an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is encoded in the plasmid" is unclear. A plasmid may comprise a DNA sequence encoding an antigen, wherein said DNA sequence is operably linked to a promoter for the expression of an effective amount of said antigen. In Amendment C filed 10/31/01 (pages 14-15), Applicants argued that an AACGTT-containing antigen-encoding plasmid (one that is based on the vector pREP7) is a species of a composition of the presently claimed invention for claiming the priority of the great-grand parent and grandparent applications. In view of the prosecution history and in view of Applicants' arguments, Applicants appear to argue that the claim encompasses a) an effective amount of an antigen in the form of a recombinant antigen, wherein the recombinant antigen is prepared from a plasmid encoded the same, and b) an effective amount of an antigen in the form of a plasmid encoding the antigen. However as recited, an effective amount of an antigen (a protein or a peptide), which is recombinant, is not per se a nucleic acid or a cDNA contained in the plasmid. Therefore, the pending claim does not reflect Applicants' intended scope. Clarification is requested regarding whether Applicants intend to claim a method wherein an antigen is a distinct component from a plasmid containing an immunostimulatory nucleic acid comprising 5'CG3' or it is a part

of said plasmid (being encoded by the plasmid). Examiner interprets the claim as a method wherein an effective amount of a recombinant antigen which is produced by a process using a plasmid encoding the same being administered into a vertebrate to treat an allergy.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on May 09, 2002 in Paper No. 35 (page 12) have been fully considered.

Applicants argued that "as recited in claim 204, an effective amount of an antigen administered through the administration of a plasmid encoding the antigen, wherein the antigen is encoded in the plasmid", and therefore it is clear that for this to occur the antigen is expressed from the plasmid in the host receiving the plasmid. Applicants' argument is found unpersuasive because the claim does not recite "an effective amount of an antigen administered through the administration of a plasmid encoding the antigen". It simply recites "an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is encoded in the plasmid". The claim does not recite that the plasmid encoding the antigen is administered into the host. Examiner interprets the claim as an effective amount of a recombinant antigen that stimulates production of allergy-associated IgE antibodies being administered into the vertebrate, wherein said antigen is produced by a process using the plasmid encoded the antigen.

Claim Rejections - 35 USC § 102

Claim 202 remain rejected under 35 U.S.C. 102(e) as being anticipated by Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995) as evidenced by Krieg et al. ((U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) for the same reasons set forth in the previous Office Action.

The claim is drawn to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is produced by a process using the plasmid.

Davis teaches the preparation of a composition for inducing an immune response in finfish comprising an expression vector having an expression control sequence capable of directing expression in finfish of at least one immunogenic polypeptide and a polypeptide encoding DNA sequence encoding at least one immunogenic polyeptide from a fish pathogen (an antigen), wherein the vector additionally comprises an immunostimulatory unmethylated CpG motif (see col. 4, lines 10-30; col. 11, lines 8-13 and the claims). Davis also teaches that multiple CpG motifs may be inserted into the non-coding region of the expression vector (col. 7, lines 23-25), and that expression vector includes purified plasmid DNA that is dissolved in an aqueous solution or in a formulation such as cationic liposomes, fluorocarbon emulsions, gold particles, biodegradable microspheres or cationic polymers which are pharmaceutically acceptable carriers (col. 8, lines 27-35). Davis further teach that the aforementioned pharmaceutical composition further comprising a second DNA vaccine, an adjuvant, a

recombinant protein (an antigen), a transfection reagent, or some combination thereof (col. 9, lines 13-20). At the effective filing date of the present application, several immunostimulatory nucleic acid sequences having the CpG motifs have been shown to activate the immune system, including the sequence comprising AACGTT as evidenced by the teachings of Krieg et al. (see Table 1 and the claims).

Therefore, the instant claim is anticipated by Davis as evidenced by Krieg et al.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on May 09, 2002 in Paper No. 35 (pages 12-13) have been fully considered.

Applicants mainly argued that claim 202 is entitled to the benefit of the great-grandparent application, August 26, 1993, therefore neither Davis nor Krieg is prior art under 35 U.S.C 102(e). Applicants' argument is not found persuasive for the reasons already stated in the priority Section. Therefore, Davis and Krieg are proper prior arts under 35 U.S.C. 102(e).

Claim Rejections - 35 USC § 103

Claims 202 and 203 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) in view of Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995) for the same reasons set forth in the previous Office Action.

The claims are drawn to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is produced by a process using the plasmid; the same wherein the plasmid is pREP7 encoding an antigen.

Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. do not teach specifically the use of an immunostimulatory unmethylated CpG motif or an immunostimulatory sequence comprising AACGTT in the form of a plasmid or more specifically in the plasmid pREP7 encoding an antigen.

At the effective filing date of the present application (January 30, 1996), Davis teaches that since copies of CpG motifs in DNA expression vectors act as adjuvants facilitating the induction of an immune response against an expression protein, multiple CpG motifs may be inserted into the non-coding region of an expression vector containing a sequence encoding an antigen (col. 7, lines 18-48; col. 11, lines 1-16). Davis further discloses that the antigen expressing vectors can be utilized concurrently

with an antigen-based vaccine such as a recombinant protein or whole-killed vaccine (col. 8, lines 16-22).

Accordingly, it would have been obvious for one of ordinary skilled artisan to modify the composition taught by Krieg et al. by specifically incorporating one or more copies of the immunostimulatory nucleic acid sequence having the unmethylated CpG motifs, including one that comprises the sequence AACGTT taught by Krieg et al. in the non-coding region of an expression plasmid vector as taught by Davis to use it as an adjuvant for a vaccine or an antigen in a pharmaceutically acceptable carrier or for an antigen encoded in the expression plasmid vector. One of ordinary skilled artisan would have been motivated to carry out the above modification because both Krieg et al. and Davis teach that unmethylated CpG dinucleotide motifs present in plasmid vectors or in free oligonucletides act as adjuvants to boost a mammal's immune response to effect better response from an antigen-based vaccine such as a recombinant protein or whole-killed vaccine or a plasmid DNA vaccine comprise a sequence encoding an antigen. Furthermore, it would also have been obvious for one of ordinary skilled artisan to use the plasmid pREP7 as an expression vector in the composition because of a designer's choice since the plasmid is publicly available from Invitrogen (Carlsbad, CA 92008 USA; Tel. No. 1-800-955-6288). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 202 and 203 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of

July 15, 1994: IDS) in view of Applicants' admission of record (Amendment C filed 10/31/01 in Paper No. 28, page 8, second last paragraph and page 9, second paragraph) for the same reasons set forth in the previous Office Action.

Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. do not teach specifically the use of an immunostimulatory unmethylated CpG motif or an immunostimulatory sequence comprising AACGTT in the form of a plasmid or more specifically in the plasmid pREP7 encoding an antigen.

However, Applicants have submitted on record that a plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides (the immunostimulatory oligonucleotides taught by Krieg et al. are in the range of between 2 to 100 base pairs, with a preferred embodiment between 8 to 40 base pairs in size), and that administering an antigen is obvious in view of administering an antigen encoded by a plasmid (see Amendment C in Paper No. 28; page 8, second last paragraph; page 9, second paragraph).

Accordingly, it would have been obvious for one of ordinary skilled artisan to modify the composition taught by Krieg et al. by introducing the immunostimulatory nucleic acid sequences having the unmethylated CpG motifs, including one that comprises the sequence AACGTT taught by Krieg et al. into a plasmid vector to use it as an adjuvant for a vaccine or an antigen in a pharmaceutically acceptable carrier. Furthermore, it would also have been obvious for one of ordinary skilled artisan to use the plasmid pREP7 as a vector in the modified composition because of a designer's choice since the plasmid is publicly available from Invitrogen (Carlsbad, CA 92008 USA; Tel. No. 1-800-955-6288). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' argument related to the above rejections in the Amendment filed on May 09, 2002 in Paper No. 35 (page13) have been fully considered.

Applicants mainly argued that claims 202-203 are entitled to the benefit of the great-grandparent application, August 26, 1993, therefore neither Davis nor Krieg is prior art under 35 U.S.C 102(e). Applicants' argument is not found persuasive for the reasons already stated in the priority Section. Therefore, Davis and Krieg are proper prior arts under 35 U.S.C. 102(e).

Following is a new ground of rejection necessitated by Applicants' amendment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claim 205 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 205 recites the limitation "the antigen encoded in the plasmid" in step (b) of the claim. There is insufficient antecedent basis for this limitation in the claim. The only antigen referred in the claim is an antigen that stimulates production of allergy-associated IgE antibodies in the mammal, not antigen encoded in the plasmid.

Claim Rejections - 35 USC § 103

New claim 206 is rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al. (U.S. Patent No. 6,214,804).

The claim is drawn to a pharmaceutical composition for stimulating an immune response to an antigen comprising pREP7 encoding the antigen and a pharmaceutically acceptable carrier.

Felgner et al. diclosed a naked polynucleotide to be injected or otherwise delivered to the animal with a pharmaceutically acceptable liquid carrier. The polynucleotides code for immunity-conferring polypeptides to provoke a humoral or cellular response or both (see cols. 9-10). Felgner et al. further teach that the polynucleotide is not limited to any particular polynucleotide coding for any particular

polypeptide, and that plasmids containing genes coding for a large number of physiologically active peptides and antigens or immunogens have been reported in the literature and can be readily obtained by those of skill in the art (col. 11, lines 1-4). Felger et al. do not specifically teach the plasmid pREP7 encoding the antigen. However, at the effective filing date of the present application, it would have been obvious for one of ordinary skilled artisan to use the plasmid pREP7 as a vector to contain a sequence encoding an immunity-conferring polypeptide in the pharmaceutical composition taught by Felgner et al. simply as a designer's choice because the plasmid vector is publicly available from Invitrogen (Carlsbad, CA 92008 USA, Tel. No. 1-800-955-6288).

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

DAVE T. NGUYEN
PRIMARY EXAMINER

Quang Nguyen, Ph.D.